IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Earl et al**

Application No: **10/612,014** Group Art Unit: **1626**

Filed: **July 3, 2003** Examiner: **Ebenezer O. Sackey**

For: **Nitrosated Nonsteroidal Antiinflammatory Compounds, Compositions and Methods of Uses**

Attorney Docket No: **102258.156 US1**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C. F. R. §1.132

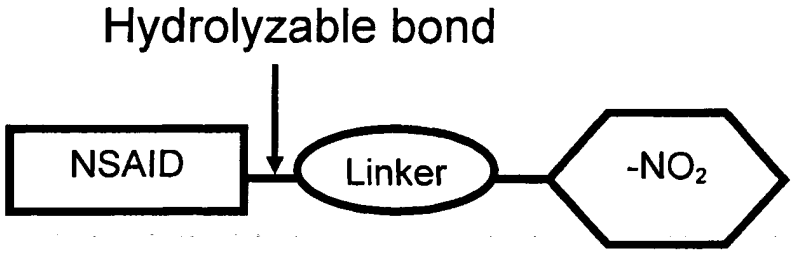
I, David S. Garvey, Ph.D. declare the following:

1. I am currently the Executive Project Director and Chief Chemistry Advisor at NitroMed, Inc. (NitroMed). From 1997 to 2003, I was the Senior Director of Chemistry at NitroMed. From 1994 to 1997, I was the Director of Chemistry at NitroMed.

2. I am a co-inventor of U.S. Application No. 10/024,040, filed July 3, 2003 (hereafter "the present application").

3. I have reviewed the specification, claims of the present application, and the Office Actions dated December 30, 2004 and June 17, 2005.

4. The present application is directed to nitrosated nonsteroidal anti-inflammatory compounds whose basic structure is depicted below:

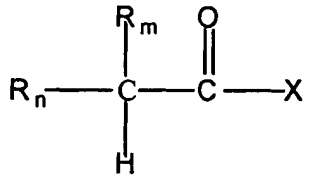


Under physiological conditions, the nitrosated nonsteroidal anti-inflammatory compounds are hydrolyzed to the parent non-steroidal anti-inflammatory compounds that retained the properties

of the original non-steroidal anti-inflammatory compounds; and a linker substituted with at least one –NO2 group that releases nitric oxide and thereby improves the side effect profile of the original non-steroidal anti-inflammatory compound.

5. In the present application, the compounds of Formula (I) are nitrosated non-steroidal anti-inflammatory compounds substituted with at least one $-NO_2$ group,

wherein the compound of Formula (I) is:



(I)

wherein R_m and R_n are as defined in the specification of the present application;

X is:

(1) $-Y-(CR_4R_4')_p-V-B-T-(CR_4R_4')_p-ONO_2$;

(2) $-Y-(CR_4R_4')_p-T-C(O)-(CR_4R_4')_o-(CH_2)-ONO_2$;

(3) $-Y-(CR_4R_4')_p-T-(CH_2)_q-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(4) $-Y-(CR_4R_4')_p-V-(CH_2)_q-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(5) $-Y-(CR_4R_4')_o-(W)_q-(CR_4R_4')_o-(CH_2)-ONO_2$;

(6) $-Y-(CR_4R_4')_p-V-(CH_2)_o-(W)_q-(CR_4R_4')_q-(CH_2)-ONO_2$;

(7) $-Y-(CR_4R_4')_p-(W)_q-(T)_o-(CR_4R_4')_o-(CH_2)-ONO_2$;

(8) $-Y-(CR_4R_4')_q-C(Z)-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(9) $-Y-(CR_4R_4')_p-V-(CR_4R_4')_p-(CH_2)-ONO_2$;

(10) $-Y-(CR_4R_4')_p-V-(CH_2)_q-(T)_o-(CR_4R_4')_q-(CH_2)-ONO_2$;

wherein

R_4 and R_4' at each occurrence are independently a hydrogen, lower alkyl group, -OH, $-CH_2OH$, $-ONO_2$, $-NO_2$ or $-CH_2ONO_2$; or R_4 and R_4' taken together with the carbon atom to which they are attached are a cycloalkyl group or a heterocyclic ring;

T at each occurrence is independently an oxygen, $(S(O)_o)_o$ or NR_j;

R_j is a hydrogen, an alkyl group, an aryl group, a heterocyclic ring, an alkylcarbonyl group, an alkylaryl group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfinyl group,

an arylsulfonyl group, a sulfonamido group, a N-alkylsulfonamido group, a N,N-diarylsulfonamido group, a N-arylsulfonamido group, a N-alkyl-N-arylsulfonamido group, a carboxamido group or a hydroxyl group;

Y is oxygen or sulfur (-S-); and

V, B, T, W, Z, p, q and o are as defined in the specification of the present application.

6. I understand that the U.S. Patent and Trademark Office examiner has rejected the claimed invention for lacking enablement such that one skilled in the art could not make and use the claimed invention without undue experimentation. Based on my understanding of the level of ordinary skill in the art of synthetic organic chemistry and my knowledge and experience of those skilled in this art, it is my opinion that one skilled in the art could readily make any and every compound that falls within the scope of the compound of Formula (I) in the present application without undue experimentation, including, but not limited to compounds, wherein R_4 and R_4' is a hydrogen, lower alkyl group, -OH, $-CH_2OH$, $-ONO_2$, $-NO_2$ or $-CH_2ONO_2$; or R_4 and R_4' taken together with the carbon atom to which they are attached are a cycloalkyl group or a heterocyclic ring and/or compounds wherein Rj in T is a hydrogen, an alkyl group, an aryl group, a heterocyclic ring, an alkylcarbonyl group, an alkylaryl group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfinyl group, an arylsulfonyl group, a sulfonamido group, a N-alkylsulfonamido group, a N,N-diarylsulfonamido group, a N-arylsulfonamido group, a N-alkyl-N-arylsulfonamido group, a carboxamido group or a hydroxyl group.

7. It is my opinion that one skilled in the art could readily make any and every compound that falls within the scope of the compounds of Formula (I) in the present application by using readily available materials, such as, for example, the commercially available parent non-steroidal anti-inflammatory compounds, in conventional reactions, in reactions that can be successfully performed by conventional modifications known to one skilled in the art, *e.g.,* by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or by the modification of reactions disclosed in the present application, without undue experimentation.

8. The detailed description of the synthesis of numerous structurally diverse nitrosated nonsteroidal anti-inflammatory compounds can be found, for example, U.S. Patent Nos. 5,859,053, 6,429,223, 6,355,666, 6,436,990, 6,525,098, 6,552,078; and in U. S. Application Nos. 2002/0028845, 2003/0088111, and in WO 94/03421, WO 94/04484, WO 94/12463, WO

95/09831, WO 95/30641, WO 96/34848, WO 97/04757, WO 97/16405, WO 98/09948, WO 98/17673, WO 98/25918, WO 00/44705, WO 00/51988, WO 00/61537, WO 00/61541, WO 00/72838, WO 01/04082, WO 01/10814, WO 01/12584, WO 01/49275, WO 01/66088, WO 02/00167, WO 02/092072, WO 02/11706, WO 02/11707, WO 02/30866, WO 02/30867, WO 02/100400, WO 03/000642, WO 03/000643, WO 03/013499, WO 03/022249; and in EP 0738706 B1, EO 0440098 A1; and in Endres et al., *Eur. J. Med. Chem*, 34: 895-901 (1999); Gilmer et al., *Eur. J. Pharm Sci.*, 16: 297-304 (2002), Gilmer et al., *Eur. J. Pharm Sci.*, 14: 221-227 (2001); and Ingram et al., *J. Pharm Pharmacol.*, 53: 345-350 (2001).

9. Additionally, one of skill in the art would certainly be able to read and understand the synthetic details in the specification of the present application. For example, page 62, line 10 to page 121, line 27, has 57 working examples with detailed experimental conditions for the preparation of compounds with numerous structurally diverse linker groups. Also the specification at, for example, page 41, line 10 to page 42, line 13, has a description with numerous literature references on how one skilled in the art could synthesis the nitrosated compounds of the invention. Based on the extensive disclosure in the specification and the state of the scientific literature for the synthesis of organic compounds, it is my opinion that one skilled in the art would easily be able to prepare any of the compounds disclosed in the specification.

10. It is my opinion that one skilled in the art will readily appreciate that the compounds of Formula (I) are pro-drugs of well known nonsteroidal anti-inflammatory compounds. The compounds of Formula (I) would be hydrolyzed under physiological conditions to the parent nonsteroidal anti-inflammatory compounds and the linker group of Formula X, substituted with at least one $-NO_2$ group.

11. It is my opinion that one skilled in the art will readily appreciate that the parent nonsteroidal anti-inflammatory compounds are well known inhibitors of the cyclooxygenase isoenzymes whose biological properties, substrate binding properties, structure activity relationship and methods of use have been extensively studied and described in numerous scientific articles. Hence it is my opinion that the biological properties of the compounds of Formula (I) would be easily predictable by one skilled in the art. For example, in a review article, Fiorucci et al, *Drug Safety*, 24: 810-811 (2001), a copy of which is attached hereto,

describe the efficacy and benefits of some nitric oxide (NO)-releasing non-steroidal anti-inflammatory compounds. At page 801, lines12-16, the authors stated:

> "NO-NSAIDs retain the anti-inflammatory and antipyretic activity of original NSAIDs, although they exhibit markedly reduced gastrointestinal toxicity. NO-NSAIDs are nonselective cyclo-oxygenase (COX) inhibitors, and they also exert COX-independent activities that are NO-dependent."

The authors concluded the article on page 810, column 1, lines 6-10, with:

> "NO-NSAIDs are a new class of anti-inflammatory drugs. Although they were originally designed to spare the GI tract, the NO moiety appears to confer a broad range of activities in these compounds."

12. It is my opinion that one skilled in the art will readily appreciate that the linker group of Formula X substituted with at least one $-NO_2$ group, under physiological conditions, would donate, release and/or directly or indirectly transfer nitric monooxide, such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

13. In summary, based on the teachings in the present application and the level of knowledge in the art, it is my opinion that one skilled in the art could readily make and use any and every compound that falls within the scope of the compound of Formula (I) without undue experimentation.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of this application or any patent issued thereon.

David S. Garvey

David S. Garvey, Ph.D.

Oct. 17, 2005

Date

LEADING ARTICLE

Drug Safety 2001; 24 (11): 801-811
0114-5916/01/0011-0801/$22.00/0

Nitric Oxide–Releasing NSAIDs

A Review of Their Current Status

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs worldwide owing to their anti-inflammatory, antipyretic and analgesic properties. However, their use is hampered by gastrointestinal (GI) toxicity, the most common drug-related serious adverse event in industrialised nations.

Nitric oxide (NO)–releasing NSAIDs, a recently described class of drugs, are generated by adding a nitroxybutyl or a nitrosothiol moiety to the parent NSAID via a short-chain ester linkage. While efficacy of nitrosothiol-NO-NSAIDs still awaits investigation, nitroxybutyl-NO-NSAIDs have been extensively studied in animals, thus the abbreviation NO-NSAIDs used here refers to the latter group of NSAID derivatives.

NO-NSAIDs retain the anti-inflammatory and antipyretic activity of original NSAIDs, although they exhibit markedly reduced gastrointestinal toxicity. NO-NSAIDs are nonselective cyclo-oxygenase (COX) inhibitors, and they also exert COX-independent activities that are NO-dependent. Indeed, NO-NSAIDs suppress production of the cytokines interleukin (IL)-1β, IL-18 and interferon-γ by causing the S-nitrosilation/inhibition of caspase-1. In acute and chronic animal models of inflammation, it has been demonstrated that NO-NSAIDs abrogated prostaglandin E_2 as well as thromboxane B_2 generation. In a murine model, NO-naproxen was approximately 10-fold more potent than naproxen in reducing animal writhing after intraperitoneal injection of acetic acid. Similar data have been obtained in chronic models of pain such as rat adjuvant arthritis. *In vivo* and *in vitro* studies suggest that NO-aspirin (acetylsalicylic acid) exerts more potent antithrombotic action than aspirin, probably by coupling the ability to inhibit COX-1 with the anti-adhesive effect of NO. Moreover, in a model of renal injury NO-flurbiprofen not only has been demonstrated to be devoid of nephrotoxicity but also to ameliorate renal function. Finally, in an animal model of chronic neurodegenerative disease, NO-flurbiprofen and NO-aspirin attenuated the brain inflammatory response. The GI toxicity of NO-flurbiprofen and NO-naproxen is currently being investigated in healthy individuals.

1. Nitric Oxide (NO): An Ubiquitous Mediator

Nitric Oxide (NO) is a highly diffusible and lipid-soluble free radical which reacts with other free radicals, oxygen, and transition metals such as iron. Binding of NO with the iron group of haemoglobin facilitates the rapid degradation of NO. The interaction between NO and oxygen results in NO_2 production which rapidly consumes more NO to form N_2O_3, an excellent nitrosating agent of thiol-containing proteins. Under normal conditions, the enzymatic sources of NO are limited to what are called the constitutive, calcium-dependent forms of NO synthase (NOS): endothelial NOS (eNOS-, type III) and neuronal NOS (nNOS, type I). The other NOS isoform is referred to as inducible NOS (iNOS, type II), which is calcium/calmodulin independent and usually occurs in states of inflammation and immune activation. iNOS is generally expressed in macrophages and neutrophils, but it can also be detected in epithelial cells.[1,2]

NO is now recognised as an important modulator of an enormous number of physiological functions. Synthesis of NO in the endothelial cells which line the inner walls of blood vessels in response to physical and chemical stimuli, has been found to play a crucial role in maintaining vasodilation and is essential for the regulation of blood pressure.[3,4] Moreover, NO inhibits aggregation and adhesion of platelets to the inner walls of blood vessels and significantly reduces the formation of blood clots. Taken together, these effects account for the major role NO plays in protecting against stroke.

In the central nervous system, NO is a neurotransmitter that underpins several functions, including the formation of memory. In the periphery, there is a widespread network of nerves, previously recognised as nonadrenergic and noncholinergic, that operate through a NO-dependent mechanism to mediate some forms of neurogenic vasodilatation and regulate various gastrointestinal (GI), respiratory and genitourinary functions. Part of these actions are mediated by the activation of soluble guanylate cyclase and the subsequent increase in the concentration of cyclic guanosine monophosphate (cGMP) in target cells.[5]

Emerging evidence suggests that some diseases are related to defects in the generation or action of NO. A polymorphism of the eNOS gene has been described recently in patients with hypertension. In addition, NO is produced in large quantities during host defence and immunological reactions.

Because it exerts cytotoxic properties and is generated by activated macrophages, NO seems to play a role in nonspecific immunity. NO also modulates the activity of bone cells (osteoblasts and osteoclasts), immune cells, endothelial cells and stromal cells. Furthermore, NO is involved in the pathogenesis of conditions such as septic shock and the hyperdynamic state of cirrhosis and in inflammation.

In the GI tract, small quantities of NO exert beneficial effects by enhancing mucosal defence, whereas high levels of NO can be detrimental. In the stomach, NO modulates epithelial fluid and mucus secretion; it is an important mediator of vascular tone of the gastric microcirculation and stimulates mucosal healing by enhancing collagen deposition by fibroblasts and by angiogenesis.[6] Moreover, NO plays a major role in gastric mucosal defense, perhaps via the inhibition of leucocyte adherence to the vascular endothelium, and protects against mucosal injury by nonsteroidal anti-inflammatory drugs (NSAIDs) and by ischaemia-reperfusion.[7] A recently published case-control study found that the use of medications that release NO, such as nitroglycerin and other nitrovasodilators, was associated with a reduction in the incidence of gastric lesions in patients taking any type of NSAID.[8]

2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Cyclo-Oxygenase (COX) Inhibition

NSAIDs are among the most widely prescribed drugs worldwide as the drugs of first choice in the treatment of rheumatic disorders and other degenerative inflammatory joint diseases. However, their use is hampered by the fact that NSAID-induced

GI toxicity is among the most common drug-related serious adverse events in industrialised nations.[7] As shown by endoscopic examinations, the prevalence of ulcers in the stomach or duodenum of patients who take NSAIDs regularly approaches 20%, and the annual incidence of clinically important lesions (i.e. GI bleeding and perforation) approaches 2%.[7,9]

NSAIDS inhibit cyclo-oxygenase (COX) and, subsequently, prostaglandin (PG) synthesis.[10] COX converts arachidonate freed from the plasma membrane by the action of phospholipase A_2 into several types of eicosanoids. It is now clear that at least 2 distinct COX isoforms exist. The constitutive isoform is termed COX-1 and is expressed in the stomach and platelets, and in fetal hearts, kidneys, lungs and brains, as well as in the decidual lining of the uterus. The inducible isoform, termed COX-2, appears during inflammation and is stimulated by potent inflammatory mediators such as the cytokines interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)γ and tumour necrosis factor (TNF)α. However, the dichotomy between COX-1, acting predominantly as a constitutive enzyme, and COX-2, acting predominantly as proinflammatory molecule, is less clear cut than what was hypothesised a few years ago. COX-1 plays a role in inflammation, and COX-2 exerts a protective role in the stomach, intestine and kidney.[11,12] In any case, with few or no exceptions, all classical NSAIDs are able to suppress both COX-1 and COX-2.

While the therapeutic anti-inflammatory effects of these agents are attributable to their ability to inhibit COX-2, their tolerability profiles correlate with inhibition of COX-1 and decreased synthesis of gastric mucosal PGs. For this reason, COX-2-selective drugs, which are associated with significantly fewer clinically important upper GI adverse events, have recently been developed.[13] Several clinical studies have shown that COX-2-selective NSAIDs cause less GI toxicity and effectively suppress inflammation.[13]

3. NO-NSAIDS

The NO-NSAIDs are a recently described class of NSAID derivatives generated by chemically coupling a NO-releasing moiety to the parent NSAID via a short-chain ester linkage (fig. 1 and table 1).[14-17] The rationale behind this coupling is that NO and nitrogen oxide compounds released from these derivatives would enhance GI mucosal defenses and prevent the pathogenic events that occur with suppression of PG synthesis, such as reduced gastric mucosal blood flow, increased TNFα plasma levels and leucocyte-endothelial cell adherence.[14-17] Thus, NO released by these compounds may counteract the detrimental effect of NSAIDs on COX inhibition.

3.1 Pharmacokinetic Properties

NO-NSAIDs exhibit markedly reduced GI toxicity, while retaining the anti-inflammatory and antipyretic activity of the parent NSAID. Animal data

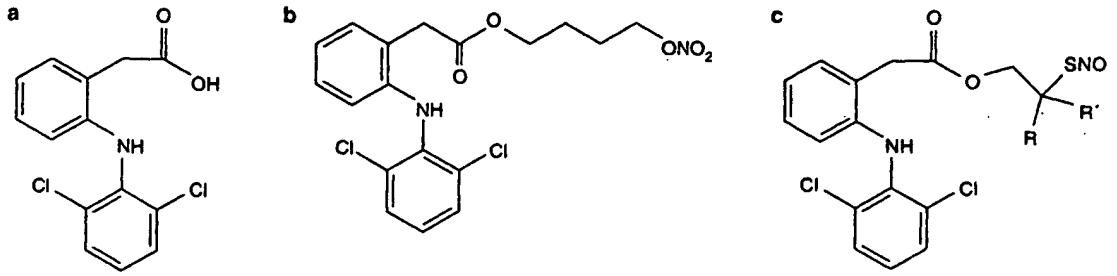

Fig. 1. Structure of diclofenac and its nitric oxide (NO)-releasing derivatives: (a) diclofenac, the parent compound; (b) nitroxybutyl diclofenac; and (c) nitrosothiol diclofenac.

Table I. Current status of nitric oxide (NO)-releasing nonsteroidal anti-inflammatory drugs in development

Drug	Company	Status
NO-aspirin (acetylsalicylic acid)[18]	Nicox	Phase I
NO-diclofenac[18]	Nicox	Preclinical
NO-naproxen[18]	AstraZeneca	Phase II
NO-ketoprofen[18]	Nicox	Preclinical
NO-flurbiprofen[18]	Nicox	Phase I
S-NO-diclofenac[19]	Nitromed	Preclinical

S-NO = nitrosothiol-nitric oxide-releasing.

demonstrate that NO-NSAIDs are metabolised differently than their parent NSAID. For example, nitrofenac, an NO-derivative of diclofenac, produces only 23% diclofenac and other metabolites measured as nitrite and nitrate.

Moreover, peak plasma concentrations of NO-NSAIDs are usually delayed compared with the parent NSAID. Nitrofenac peaks 7 hours after drug administration, while diclofenac has 3 peaks at 2, 5 and 10 hours.[15] Preliminary data indicate that after their absorption, NO-NSAIDs such as nitrofenac, NO-naproxen and NO-aspirin (acetylsalicylic acid) dissociate into 2 components, the parent NSAID and the NO-releasing derivative. Indeed, NO-aspirin administration results in a time-related increase in plasma nitrate/nitrite and salicylate concentrations. It has been demonstrated in humans and animals that hydrolysis of NO-aspirin might occur in the GI wall and fluids, and during the first pass of NO-aspirin through the liver.[14,16] Because the initial cleavage of NO-aspirin is relatively slow, the time required to obtain the salicylate peak plasma concentration after NO-aspirin administration is doubled compared with aspirin (6 and 3 hours, respectively), but the elimination rate of salicylic acid is similar for both compounds.[14,16] However, it is unlikely that this difference in NO-NSAIDs pharmacokinetics explains the reduced toxicity of these drugs, although it may account for the lack of hypotension seen with these compounds compared with equimolar doses of a standard NO donor.[16]

A potential limitation of NO-NSAIDs arises from their intrinsic nature as indirect sources of NO, suggesting that repeated administration of NO-NSAIDs may cause tolerance, a phenomenon frequently observed in nitrate-taking NSAIDs. This issue is particularly relevant for nitrosothiol-NO-NSAIDs. Indeed, this class of NO-NSAIDs is generated by adding a nitrosothiol (S-NO) moiety to conventional NSAIDs (such as diclofenac) through an ester linkage. These S-NO-NSAIDs, similarly to endogenous S-nitrosothiol compounds, act as NO donors without the need for metabolic transformation.[17,19,20] It is known that S-nitrosothiols can directly modulate cell physiology through S-transnitrosation reactions, by which the NO group is effectively transferred from the S-nitrosothiol to the thiol of a target biomolecule in exchange for a hydrogen.[21] Although nitrosothiol catabolism is incompletely understood, transition metal-dependent redox processes and/or enzyme-catalysed decompositions likely predominate biological pathways for NO release from nitrosothiols *in vivo*.

Oral administration of all forms of S-NO-diclofenac esters deliver diclofenac to the plasma to varying degrees, likely depending upon some salient structural features, particularly the chain length of the alkyl spacer and the substituent at the tertiary amine group. In all cases, however, plasma diclofenac levels peak within 30 minutes following oral administration, as would be expected if the S-NO-diclofenac esters were NSAID prodrugs *in vivo*. Comparable with the other NO-NSAIDs, these compounds exert anti-inflammatory activity similar to the parent NSAID, but are devoid of apparent GI toxicity.[21]

3.2 Mechanism of Action

NO-releasing NSAIDs are nonselective COX inhibitors. Their efficacy in reducing pain and inflam-

mation is largely attributable to suppression of PG synthesis. However, an increasing body of evidence indicate that NO-coupled NSAIDs exert COX-independent activities.[22-25] Indeed, we have recently demonstrated that NCX-4016, a NO-aspirin derivative, inhibits caspase activity and exerts anti-apoptotic and anti-inflammatory effects by reducing proinflammatory cytokine generation (fig. 2).[24]

Caspases are a family of intracellular cysteine proteases that share sequence homology with *Ced-3*, a nematode gene involved in the execution phase of apoptosis.[25] The mammalian counterparts of the *Ced-3* gene products include at least 14 different endoprotease that have been renamed caspases to denote cysteine proteases acting after an aspartic acid residue. Caspase-1 denotes the original IL-1 converting enzyme (ICE) that cuts the IL-1β and IL-18 (or IFNγ inducing-factor) precursor into an active mature form and has the greatest specificity for cleaving pro-IL-1β and pro-IL-18. The comparison of molecular structures suggests that the caspase family falls into 3 major groups. These include caspases that function primarily in cytokine maturation (e.g. caspase-1, -4 and -5); initiator caspases, involved in signalling early steps of extracellular regulated apoptosis (e.g. caspase-8, -9 and -10); and effector proteases involved in the execution phase of apoptosis (e.g. caspase-3, -6 and -7).

In support of this caspase functional specialisation, specific ICE inhibitors administered to mice exert poor anti-apoptotic effects, although they reduce inflammation as effectively as does blocking IL-1β activity with specific antagonists. In the past few years we have provided evidence that NCX-4016 inhibits the release of the proinflammatory cytokines (IL-1β, IL-18 and IFNγ) *in vitro* and *in vivo* through a mechanism that involves the S-nitrosylation/inhibition of proteases required for cellular processing/maturation of IL-1β and IL-18.[23] This effect is COX-independent since it cannot be reproduced by selective and nonselective COX-1 and/or COX-2 inhibitor. The mechanism through which NCX-4016 inhibits cytokine generation is largely dependent on the ability of this compound to inhibit ICE-like cysteine proteases involved in cutting pro-IL-1β and pro-IL-18.[21-25]

Likewise, endogenous NO derived from eNOS and/or iNOS inhibits T helper cell 1-type cytokine

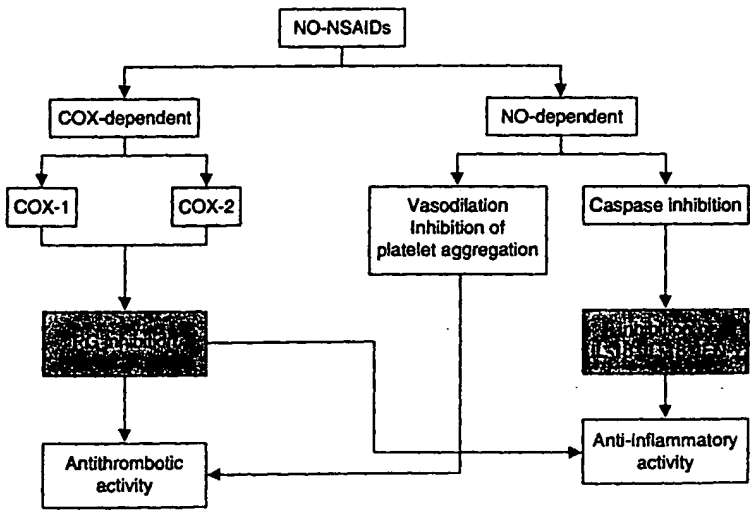

Fig. 2. Mechanism of action of nitric oxide (NO)-releasing nonsteroidal anti-inflammatory drugs (NSAIDs). NO-NSAIDs act via cyclo-oxygenase (COX)-dependent and COX-independent, NO-dependent mechanisms. Inhibition of cytokine generation may also contribute to their anti-inflammatory activity. IL = interleukin; IFNγ = interferon gamma; PG = prostaglandin.

production *in vitro* and *in vivo*. Selective ICE inhibitors have recently been demonstrated to be effective in reducing inflammation in patients with rheumatoid arthritis,[26] and caspase inhibitors are being developed by various pharmaceutical companies as anti-inflammatory and anti-apoptotic drugs. However, these anti-apoptotic compounds have consistent limitations due their intrinsic toxicity.[26] The fact that NO-NSAIDs inhibit caspase activity raises the possibility that they might have, in contrast to conventional NSAIDs, disease-modifying properties. The ability to inhibit proinflammatory and pro-apoptotic caspases is likely responsible for the extended range of activities of NO-NSAIDs in comparison with parent compounds.

4. Effects on the Gastrointestinal Tract

Our knowledge about the GI safety of NO-NSAIDs is mainly derived from animal studies. Available data show that NO-releasing NSAIDs spare the GI mucosa and that, at least in rats, any dosage of nitrofenac, nitrosodiclofenac, NO-naproxen, NO-flurbiprofen, NO-ketoprofen or NO-aspirin, causes significantly less gastric mucosal injury than standard NSAIDs.[14-17,19-25] A similar reduction of GI toxicity is observed if the compounds are given parenterally rather than orally, suggesting that the reduced injury is not simply attributable to reduced topical irritant properties.

Animal studies have demonstrated that NO-NSAIDs spare the stomach yet also inhibit gastric mucosal COX activity.[23,27-30] These results suggest that mechanisms other than PG inhibition are responsible for GI protection. Indeed, it has been demonstrated that topical application of NO-aspirin to the stomach markedly increased rat gastric mucosal blood flow, which remained significantly elevated for 30 minutes after removal of the NO-compound and did not exert any effect on potential difference and pH.[21,26-31] The administration of other NO-NSAIDs (NO-diclofenac and NO-flurbiprofen) induces the same effect on mucosal blood flow, suggesting that NO-NSAIDs are capable of protecting the GI mucosa from injury, possibly through preservation of mucosal blood flow.

Despite the effect of NO-NSAIDs on gastric microcirculation, it is noteworthy that, in experimental animals, they do not alter systemic arterial blood pressure, even when administered intravenously, in large doses or when administered during an experimental model of endotoxic shock.[14,30] In contrast, an equimolar dose of a conventional NO donor causes a profound hypotension. Although after NO-NSAIDs administration there is a significant increase in nitrate/nitrite plasma levels consistent with the release of NO in the systemic circulation, the absence of a hypotensive effect can be explained by the fact that the kinetics of hydrolysis of NO-compounds is very slow.

Not only are NSAIDs by themselves ulcerogenic in the stomach, but they also potentiate the ulcerogenic response to various stimuli, including stress. It has been demonstrated that, unlike aspirin, NO-aspirin does not potentiate the gastric ulcerogenic response to stress and confers a dose-dependent protection against hydrochloric acid- and ethanol-induced gastric damage.[28] Taken together, these data suggest that NO-NSAIDs are devoid of topical irritant action, are not ulcerogenic and do not potentiate the gastric ulcerogenic response to stress.[26] The absence of toxic GI effects is also confirmed in either normal or diabetic rat stomachs, which are known to be more vulnerable to NSAID-induced damage.[27]

Concerning the mechanism responsible for the lower rates of GI toxicity with NO-NSAIDs, we have recently demonstrated, *in vivo* and *in vitro*, that NO-aspirin protects the stomach by inhibiting gastric mucosal cell apoptosis and caspase activity (see section 3.2)[22]

Currently, 2 NO-NSAIDs, NO-flurbiprofen and NO-naproxen are being evaluated for GI toxicity in healthy volunteers. Thus far, the former compound was found to be significantly less injurious than flurbiprofen in healthy volunteers.[32] Data on NO-naproxen have not yet been published.

5. Effects on Renal Function

NSAIDs can severely depress glomerular filtration rate in patients with chronic renal failure by

inhibiting the synthesis of vasodilator PGs. Chronic NO inhibition leads to progressive arterial hypertension, glomerular ischaemic injury, glomerulosclerosis and interstitial inflammation, suggesting that the haemodynamic and cellular effects of NO are essential to maintain renal integrity and circulatory homeostasis.

NO-NSAIDs have reduced renal toxicity compared with parent NSAIDs.[33] Indeed, it has been demonstrated that NO-flurbiprofen is devoid of nephrotoxicity and ameliorates structural injury in remnant kidney of rats after surgical reduction of renal mass.[33] However, the mechanism underlying these protective effects are still unclear. It can be speculated that NO-flurbiprofen acts as a kidney NO donor, as indicated by the increase of the urinary excretion of nitrite/nitrate.[33,34]

6. Effects on Platelet Aggregation

Aspirin is a widely prescribed agent with antithrombotic effects at lower dosages (75 to 320 mg/day) than that necessary for anti-inflammatory activity. The antithrombotic effect of aspirin is attributable to its ability to irreversibly block thromboxane A_2 (TxA_2) in platelets, thus preventing platelet aggregation and vasoconstriction. However, even at antithrombotic doses, aspirin is associated with increased risk of GI damage.[35] Thus, it is clear that despite the effectiveness of prophylactic aspirin treatment in reducing major cardiovascular events, alternative antithrombotic drugs with lower risk of GI adverse effects are needed.

NO-aspirin, specifically NCX-4016, which spares the GI tract, is approximately 7 times more potent than aspirin as an inhibitor of thrombin-induced human platelet aggregation *in vitro*.[17] In *ex vivo* studies of ADP-, collagen- or thrombin-induced rat platelet aggregation, aspirin and NO-aspirin have been found to have comparable inhibitory effects.[17] Despite the fact that NO-aspirin inhibits platelet TxA_2 synthesis similarly to aspirin, this NO-NSAID has enhanced antithrombotic activity, suggesting that NO-aspirin inhibits platelet aggregation either by COX-1 inhibition or NO release.[17,36] In fact, haemoglobin, an NO-chelating agent, partially reverses the effect of NO-aspirin on platelet aggregation.

It is known that NO, by activating soluble guanylyl cyclase, acts primarily on the early phase of platelet activation,[17,36] thus modulating the expression of adhesion molecules. NO-aspirin, but not aspirin, at concentrations ranging from 2.5 to 500 μmol/L inhibits platelet adhesion by modulating the expression of these adhesion receptors. Moreover, in a manner similar to nitroprusside, NO-aspirin increases platelet cGMP levels and reduces the cellular calcium increase induced by thrombin. These data suggest that NO-aspirin has an anti-adhesive effect linked to the NO release.

7. Effects on Pain

The major indication for prescribing an NSAID is the treatment of pain. NO-NSAIDs, particularly NO-naproxen and NO-flurbiprofen, inhibit COX-1 and COX-2 and, therefore, their analgesic effect is largely dependent on the suppression of these COX activities. However, in several animal models NO-NSAIDs have demonstrated an increased analgesic activity in comparison with conventional NSAIDs, raising the question of whether additional mechanisms are involved in this effect. In a model of acute pain induced by intraperitoneal injection of acetic acid in mice, NO-naproxen was found approximately 10-fold more potent than naproxen in reducing animal writhing.[28] Similar data have been obtained in more chronic models of pain such as adjuvant arthritis in rats.[37,38]

8. Effects on Inflammation

The biological activity of NO-flurbiprofen and NO-naproxen has been evaluated in different experimental models of acute inflammation. In the zymosan-induced peritonitis model, polymorphonuclear leucocyte accumulation in the peritoneum was unaffected by flurbiprofen or NO-flurbiprofen (HCT-1026).[39] However, monocyte recruitment was selectively affected by NO-naproxen (49.6% inhibition), but not by flurbiprofen. Flurbiprofen and NO-flurbiprofen suppressed PGE_2 production in 4-hour inflammatory exudates as well as TxB_2 gen-

eration by activated platelets.[29,36,37] Similar results have been obtained with NO-naproxen in acute and chronic models of inflammation.[37] It is likely that the ability to suppress cytokine production is the underlying mechanism responsible for the increased anti-inflammatory potency of NO-aspirin in comparison with aspirin (see section 3.2).[23,37,38]

9. Effects in Neurodegenerative Disorders

Alzheimer's disease is associated with a distinct pattern of neuropathological changes and a dense distribution of highly activated astrocytes and microglia. Another pathological hallmark of Alzheimer's disease is increased levels of the pro-inflammatory cytokines, IL-1β, IL-6 and TNFα. Thus, it is not surprising that conventional NSAIDs have been shown to slow the progress, or delay the onset of Alzheimer's disease.[40] In addition, recent evidence suggested that neuronal COX-2 is elevated in the brains of patients with Alzheimer's disease, which suggests that long term inhibition of this enzyme might underlie the beneficial effects of NSAIDs in these patients.

In an animal model of brain inflammation, NO-flurbiprofen and NO-aspirin administered peripherally attenuated the extensive brain inflammation induced by continuous infusion of lipopolysaccharide (LPS) into the fourth ventricular space of the rat brain for 30 days.[41-43] Daily administration of NO-flurbiprofen (1, 5 and 15 mg/kg) significantly, and in a dose-dependent manner, attenuated brain inflammation as indicated by decreased density and reactivity of microglial cells. Daily administration of NO-aspirin (100 mg/kg) also attenuated the brain inflammation, but to a much lesser degree than NO-flurbiprofen.[41,42] These results suggest that NO-NSAIDs could reduce brain inflammation in rat model of brain inflammation.

In other experiments, NO-NSAIDs seem to protect from memory lost in Alzheimer's disease model.[41-43] Chronic LPS infusions impaired performance of young rats but not adult or old rats. Daily treatment with NO-flurbiprofen (15 mg/kg subcutaneously) improved the performance of LPS-infused young rats, but not LPS-infused adult or old rats. LPS infusions increased the number of activated microglia in young and adult rats but not old rats. NO-flurbiprofen treatment attenuated these changes. These results suggest that NO-NSAID therapies designed to influence the onset of Alzheimer's disease should be initiated in adults before age-associated inflammatory processes develop within the brain.

10. Effects on Bone

Bone remodelling depends on the coupled activity of osteoclasts, which are responsible for bone resorption and osteoblasts, which are associated with the bone formation. It has been demonstrated that eNOS is expressed in both osteoblasts and osteoclasts.[44] Since osteoblasts are significantly more abundant in bone and apparently express higher eNOS levels, their NO production is quantitatively more prevalent. As in other tissues, eNOS seems to be the main isoform expressed in bones in the basal state, while iNOS is expressed in osteoblasts during inflammation and is likely to be the main source of NO.

It has been shown that NO modulates the activity of both osteoblasts and osteoclasts *in vitro*. Moreover, a number of studies suggests that NO may have an anabolic effect on bone tissue.[44] Thus, NO donors increase osteocalcin synthesis and the formation of a mineralised matrix by osteoblasts *in vitro*, while NOS inhibitors have an antiproliferative effect on osteoblastic cells *in vitro*. On the other hand, the release of large amounts of NO by cytokine-stimulated cells may have an antiproliferative effect on osteoblasts. Therefore, NO appears to have a biphasic effect on bone forming cells: at low concentrations it promotes bone formation, whereas at high concentrations NO has an inhibitory effect on osteoblasts. Similarly, both stimulatory and inhibitory effects have also been reported in osteoclasts.

Based on this evidence, NO-NSAIDs have been tested *in vivo* to investigate their potential to treat or prevent bone loss. These preclinical studies have demonstrated that NO-flurbiprofen is significantly

more potent than flurbiprofen in inhibiting IL-1β release from murine osteoblast/bone marrow co-culture assay.[45,46] Since osteoblast-derived IL-1β is essential for osteoclast activation, it might be speculated that NO-flurbiprofen inhibits osteoclast formation by acting on bone-remodelling cytokines. Confirming this view, the NO-flurbiprofen effectively protected against bone mass loss induced by ovariectomy in mice.[45,46] Taken together, these data suggest that NO-flurbiprofen could be of clinical value in the treatment of bone diseases.

11. Effects on Neoplastic Cells

Numerous reports from human epidemiological studies, animal models, and *in vitro* cell culture experiments have suggested that NSAIDs may potentially be chemopreventive agents.[1] The only common denominator for the broad spectrum of nonspecific and COX-2-specific effects of the NSAIDs with chemopreventive potential is the ability to inhibit COX-2.[47] However, it is possible that non-COX actions could also be important targets of the antineoplastic effect of these drugs. Thus, the identification of the non-COX 2 pathways may reveal promising new targets for the design of antineoplastic agents. Hanif et al.,[48] observed that extremely high concentrations of sulindac sulfide and piroxicam decreased proliferation and increased apoptosis in both HCT-15 and HT29 cell lines. Supporting this view, it has been demonstrated that the NO-aspirin derivative NCX-4016, without suppressing systemic COX-1 and COX-2 activity, reduced the number of aberrant crypt foci in an animal model of colon cancer and exhibited chemopreventive effects superior to aspirin.[49] More recently the effect of NO-aspirin, NO-sulindac, and NO-ibuprofen has been tested on cultured HT-29 colon adenocarcinoma cells, and the authors have reported that NO-NSAIDs, by inducing apoptosis, reduce cell growth much more effectively than the corresponding NSAIDs.[50] Their superior effectiveness compared with traditional NSAIDs, makes NO-NSAIDs promising candidates for chemopreventive agents against colon cancer.

12. NO-Paracetamol (Acetaminophen)

Currently, paracetamol (acetaminophen) is a first-line agent for pain management and antipyresis in a variety of patients, including children, pregnant women and those with osteoarthritis and noninflammatory musculoskeletal conditions. Although paracetamol is not a true NSAID, it possesses part of the complement of NSAID therapeutic actions (analgesia and antipyresis), but it is devoid of anti-inflammatory and antithrombotic activity. When administered to humans, it reduces levels of PG metabolites in urine but does not reduce synthesis of PGs by blood platelets or by the stomach mucosa.[51]

Paracetamol is a weak inhibitor of COX-1 and COX-2 and displays some selectivity toward COX enzymes from different organs. Thus, it is a more potent inhibitor of COX from dog and rabbit brain than that those from dog spleen. The *in vitro* activity of paracetamol also depends on the addition of co-factors (e.g. in the presence of glutathione and hydroquinone, paracetamol inhibited COX activity). Recently, a variant of COX-2, known as COX-3, that is induced by high concentrations of the NSAID diclofenac and is more susceptible to inhibition by paracetamol than either COX-1 or COX-2, has been identified.[49] Inhibition of NSAID-induced COX activity by paracetamol but not aspirin, coupled with reduced sensitivity to competitively acting NSAIDs, suggests that large changes in the COX-2 active site have occurred because of chronic NSAID treatment.[51] Therefore, COX-3 may be a product of the same gene that encodes COX-2, but has specific and distinct enzymatic activities.

Owing to its relatively high safety profile and a low incidence of adverse effects, paracetamol is one of the most widely used analgesics, both in adults and children. However, paracetamol has been associated with hepatotoxicity, usually as a result of deliberate self-poisoning or accidental overdose. Nitroparacetamol (NCX-701), a newly synthesised NO-paracetamol, exhibits augmented antinociceptive activity in both rats and mice and exerts anti-inflammatory effects over the same dose range.[32] Moreover, high dosages of NO-paracetamol did not cause liver damage in mice.[52] These results in-

dicate that NO released from NO-paracetamol might exert hepatoprotective effects, suggesting that the drug may be considered a safer alternative to paracetamol in specific clinical conditions.

13. Conclusions

NO-NSAIDs are a new class of anti-inflammatory drugs. Although they were originally designed to spare the GI tract, the NO moiety appears to confer a broad range of activities to these compounds. NO-NSAIDs appear to exert their effect either through COX-dependent and COX-independent, NO-mediated pathways. The ability to inhibit ICE-regulated cytokines might explain the increased potency of these compounds in reducing inflammation. Together with the lack of hepato- and nephrotoxicity in animals, the lower incidence of GI toxicity with NO-NSAIDs suggests that clinical use of these drugs could contribute to reducing the burden of adverse events associated with selective and nonselective COX inhibitors. Clinical trials are indicated before the definitive role of NO-NSAIDs can be determined.[53]

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CHAPTER

26 ANALGESIC–ANTIPYRETICS AND ANTIINFLAMMATORY AGENTS; DRUGS EMPLOYED IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND GOUT

Paul A. Insel

In this chapter drugs that are antiinflammatory, analgesic, and antipyretic will be considered; their mechanisms of action differ from those of the antiinflammatory steroids and the opioid analgesics. Also discussed are certain drugs (*e.g.*, gold compounds and others) that may modify the progression of rheumatoid arthritis, although they are not antiinflammatory in the classical sense. Finally, drugs used in the treatment of gout, such as colchicine and allopurinol, are discussed. Several other agents are employed to suppress the manifestations of inflammation but are described in other sections of the textbook. These include the adrenocorticosteroids, antagonists of histamine and 5-hydroxytryptamine, and immunosuppressive agents.

The antiinflammatory, analgesic, and antipyretic drugs are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and side effects. The prototype is aspirin; hence these compounds are often referred to as *aspirin-like drugs;* they are also frequently designated as *nonsteroidal antiinflammatory drugs* (NSAIDs).

There has been substantial progress in elucidating the mechanism of action of aspirin-like drugs, although a precise understanding of their therapeutic activities and side effects is still lacking. Inhibition of cyclooxygenase, the enzyme responsible for the biosynthesis of the prostaglandins and certain related autacoids, is generally thought to be a major facet of the mechanism of action of aspirin-like drugs. Some of their shared properties will first be considered; then the more important drugs will be discussed in some detail.

History. The medicinal effect of the bark of willow and certain other plants has been known to several cultures for centuries. In England in the mid-eighteenth century, Reverend Edmund Stone described in a letter to the president of the Royal Society "an account of the success of the bark of the willow in the cure of agues" (fever). Since the willow grew in damp or wet areas "where agues chiefly abound," Stone reasoned that it would probably possess curative properties appropriate to that condition.

The active ingredient in the willow bark was a bitter glycoside called *salicin,* first isolated in a pure form in 1829 by Leroux, who also demonstrated its antipyretic effect. On hydrolysis, salicin yields glucose and salicylic alcohol. The latter can be converted into salicylic acid, either *in vivo* or by chemical manipulation. Sodium salicylate was first used for the treatment of rheumatic fever and as an antipyretic in 1875, and the discovery of its uricosuric effects and of its usefulness in the treatment of gout soon followed. The enormous success of this drug prompted Hoffman, a chemist employed by Bayer, to prepare acetylsalicylic acid based on the earlier, but forgotten, work of Gerhardt in 1853. After demonstration of its antiinflammatory effects, this compound was introduced into medicine in 1899 by Dreser under the name of *aspirin.* The name is said to have been derived from *Spiraea,* the plant species from which salicylic acid was once prepared.

The synthetic salicylates soon displaced the more expensive compounds obtained from natural sources. By the early years of this century the chief therapeutic actions of aspirin were known. Toward the end of the nineteenth century, other drugs were discovered that shared some or all of these actions; among these, only derivatives of para-aminophenol (*e.g.*, acetaminophen) are used today. Beginning with indomethacin, a host of new agents has been introduced into medicine in various countries during the past 20 years.

MECHANISM OF ACTION OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Although this class of drugs had been known to inhibit a wide variety of reactions *in vitro*, no convincing relationship could be established with their known antiinflammatory, antipyretic, and analgesic effects. In 1971, Vane and associates and Smith and Willis demonstrated that low concentrations of aspirin and indomethacin inhibited the enzymatic production of prostaglandins (*see* Chapter 24). There was, at that time, some evidence that prostaglandins participated in the pathogenesis of inflammation and fever, and this reinforced the hypothesis that inhibition of the biosynthesis of these autacoids could explain a number of the clinical actions of the drugs (*see* Higgs *et al.*, in Symposium, 1983a). Numerous subsequent observations have solidified this point of view, including the discoveries that prostaglandins are released whenever cells are damaged, they appear in inflammatory exudates, and nonsteroidal antiinflammatory drugs inhibit the biosynthesis and release of prostaglandins in all cells tested. However, the nonsteroidal antiinflammatory drugs do not generally inhibit the formation of eicosanoids such as the leukotrienes, which also contribute to inflammation, nor do they affect the synthesis of numerous other inflammatory mediators. Furthermore, these drugs may have other actions that contribute to their therapeutic effects in the treatment of rheumatoid arthritis (*see* below).

Inflammation. The inflammatory process involves a series of events that can be elicited by numerous stimuli (*e.g.*, infectious agents, ischemia, antigen–antibody interactions, and thermal or other physical injury). Each type of stimulus provokes a characteristic pattern of response that represents a relatively minor variation on a theme. At a macroscopic level, the response is usually accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia), and pain. Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms: (1) an acute transient phase, characterized by local vasodilatation and increased capillary permeability; (2) a delayed, subacute phase, most prominently characterized by infiltration of leukocytes and phagocytic cells; and (3) a chronic proliferative phase, in which tissue degeneration and fibrosis occur.

Many mediators of the inflammatory process have been identified. Histamine was one of the earliest candidates, and several H_1 antagonists have long been available; however, they are useful only for the treatment of vascular events in the early transient phase of inflammation (*see* Chapter 23). Bradykinin and 5-hydroxytryptamine (5-HT) may also have a role, but their antagonists also ameliorate only certain types of inflammatory responses (*see* Chapter 23). There has been a considerable effort to develop effective inhibitors of the formation or action of the leukotrienes, but their clinical usefulness has yet to be determined. Another lipid autacoid, platelet-activating factor (PAF), has recently been indicted as an important mediator of inflammation, and inhibitors of its synthesis and action are under study (*see* Chapter 24).

The effects produced by intradermal, intravenous, or intraarterial injections of small amounts of prostaglandins are strongly reminiscent of inflammation. Prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) cause erythema and an increase in local blood flow. With PGE_2, such effects may persist for up to 10 hours, and they include the capacity to counteract the vasoconstrictor effects of substances such as norepinephrine and angiotensin. These properties are not generally shared by other inflammatory mediators. In contrast to their long-lasting effects on cutaneous vessels and superficial veins, prostaglandin-induced vasodilatation in other vascular beds vanishes within a few minutes.

Although PGE_1 and PGE_2 (but not $PGF_{2\alpha}$) cause edema when injected into the hind paw of rats, it is not clear if they can increase vascular permeability (leakage) in the postcapillary and collecting venules without the participation of other inflammatory mediators (*e.g.*, bradykinin, histamine, leukotriene C_4). In addition, there is a clear synergism between PGE_1 and bradykinin when these two compounds are given together. Prostaglandins are also unlikely to be directly involved in chemotactic responses, even though they may promote the migration of leukocytes into an inflamed area by increasing blood flow. One potent chemotactic substance, leukotriene B_4, is a product of the lipoxygenase pathway of arachidonate metabolism (*see* Chapter 24; Larsen and Henson, 1983). Although high concentrations of aspirin-like drugs can inhibit cell migration, inhibition of lipoxygenase does not appear to be involved.

Rheumatoid Arthritis. Although the pathogenesis of rheumatoid arthritis is largely unknown, it is generally agreed that it represents an autoimmune disease that involves both the humoral and cellular arms of the immune response (*see* Zvaifler, 1988; Cooke and Scudamore, 1989). A complex interaction of genetic, immunological, and local factors has been invoked to account for the differing patterns of joint involvement and progression of disease among patients with rheumatoid arthritis; viral or other infections may also be involved in the initiation and/or exacerbations of the disease. The process is thought to be initiated by a hypothetical joint-seeking ("arthrotropic") antigen that is processed and presented by macrophages to T lymphocytes in conjunction with a major histocompatibility antigen in the synovial membrane. The

interaction of this complex with T-cell receptors, together with the actions of macrophage-derived cytokines, results in the activation, differentiation, and clonal expansion of T cells. These elements of the cellular immune response are accompanied by microvascular injury and an inflammatory reaction that includes development of an exudative synovial fluid that contains many neutrophils. Although activation of B lymphocytes and the humoral immune response is also clearly evident, most of the antibodies that are generated are IgGs of unknown specificity that apparently arise from polyclonal activation of B cells, rather than from a response to a specific antigen. Some of the antibodies are IgMs that are directed against determinants in the Fc fragment of IgG (rheumatoid factors); their concentration in the systemic circulation often parallels the intensity of articular disease.

Although this scenario does not adequately explain the persistence of rheumatoid arthritis and the fluctuations in its intensity that are observed in many patients, the notion that activated T cells "drive" the process is consistent with a number of observations (*see* Lipsky *et al.*, 1989). These include the presence of large numbers of activated memory ($CD4^+$) T cells and of T cell–derived cytokines in synovial tissue or fluid, improvement of patients after thoracic duct drainage or total lymphoid irradiation, and the therapeutic effects of cyclosporine and the cytotoxic agents (*e.g.*, methotrexate, cyclophosphamide). However, other cells and their products are likely to be involved in the perpetuation of disease and may also exert inhibitory or immunosuppressive effects that may be partially responsible for fluctuations in its intensity. Nevertheless, the reasons for persistence and fluctuation of rheumatoid inflammation are poorly understood. Competing ideas include persistent antigenic stimulation with cycles of positive and negative responses; alternatively, there may be repeated introduction of antigens into the synovium, each followed by the evolution and resolution of an immune reaction.

Many cytokines have been found in the rheumatoid synovium (*see* Lipsky *et al.*, 1989); one of the most prominent of these is interleukin-1 (IL-1). Increased concentrations of IL-1 are present in the plasma of patients with active rheumatoid arthritis and may be partially responsible for some of the systemic manifestations of the disease. IL-1 is released from many cells (most notably mononuclear phagocytes) in response to physical or chemical activation of the inflammatory process and appears to have a central role in both humoral and cellular immune reactions (*see* Dinarello, 1988).

Although some of the effects of IL-1 may be regarded as antiinflammatory (*e.g.*, increased production of gamma-interferon), other actions promote inflammation; these include mobilization of polymorphonuclear leukocytes from bone marrow and stimulation of their function, stimulation of the production of lymphokines by T lymphocytes, and promotion of adherence of leukocytes to endothelial cells. Other actions of IL-1 contribute to the fibrosis and tissue degeneration of the chronic proliferative phase of inflammation; these include stimulation of fibroblast proliferation, induction of collagenase by chondrocytes and synovial cells, and activation of osteoblasts/osteoclasts.

Of the available antiinflammatory drugs, only the adrenocorticosteroids are known to interfere with the synthesis and/or actions of cytokines such as IL-1 or tumor necrosis factor (*see* Chapter 60). Although some of the actions of these cytokines are accompanied by the release of prostaglandins and/or thromboxane A_2, only their pyrogenic effects are blocked by inhibitors of cyclooxygenase (*see* below). In addition, many of the actions of the prostaglandins are inhibitory to the immune response, including suppression of the function of helper T cells and B cells and inhibition of the production of IL-1. Thus, it is difficult to ascribe the antirheumatoid effects of aspirin-like drugs solely to inhibition of prostaglandin synthesis. It has been proposed that salicylate and certain other aspirin-like drugs can directly inhibit the activation and function of neutrophils, even though prostaglandins exert similar inhibitory activity (*see* Weissmann, in Symposium, 1987a). However, high concentrations of the drugs are required for such effects to be manifest *in vitro*, and the relationship of these observations to therapeutic responses to the drugs remains controversial.

Pain. The aspirin-like drugs are usually classified as mild analgesics, but this classification is not altogether correct. A consideration of the type of pain as well as its intensity is important in the assessment of analgesic efficacy. In some forms of postoperative pain, for example, the aspirin-like drugs can be superior to the opioid analgesics. Moreover they are particularly effective in settings in which inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli.

Prostaglandins are associated particularly with the development of pain that accompanies injury or inflammation. Large doses of PGE_2 or $PGF_{2\alpha}$, given to women by intramuscular or subcutaneous injection to induce abortion, cause intense local pain. Prostaglandins can also cause headache and vascular pain when infused intravenously. Although the doses of prostaglandins required to elicit pain are high in comparison with the concentrations expected *in vivo*, sensitization to painful stimuli (hyperalgesia) occurs when even minute amounts of PGE_1 are given intradermally. Moreover, subdermal infusion of mixtures of PGE_1 with small, subthreshold amounts of either bradykinin or histamine causes marked pain.

The capacity of prostaglandins to sensitize pain receptors to mechanical and chemical stimulation has been confirmed by electrophysiological measurements and appears to result from a lowering of the threshold of the polymodal nociceptors of C fibers (Perl, 1976). In general, the aspirin-like drugs do not affect the hyperalgesia or the pain caused by direct action of prostaglandins, consistent with the notion that it is their synthesis that is inhibited.

Fever. Regulation of body temperature requires a delicate balance between the production and loss

of heat, and the hypothalamus regulates the set point at which body temperature is maintained. In fever, this set point is elevated, and aspirin-like drugs promote its return to normal. These drugs do not influence body temperature when it is elevated by such factors as exercise or increases in the ambient temperature.

Fever may be a result of infection or one of the sequelae of tissue damage, inflammation, graft rejection, malignancy, or other disease states. A common feature of these conditions is the enhanced formation of cytokines such as IL-1 or tumor necrosis factor by neutrophils and other cells; this induces the synthesis of PGE_2 in vascular organs in the preoptic hypothalamic area. The prostaglandin acts within the hypothalamus to produce the resultant elevation of body temperature by processes that appear to be mediated by cyclic AMP. Aspirin-like drugs suppress this response by inhibiting the synthesis of PGE_2 (Dascombe, 1985; Stitt and Nadel, 1986). The evidence for this scenario includes the ability of prostaglandins, especially PGE_2, to produce fever when infused into the cerebral ventricles or when injected into the hypothalamus. In addition, fever is a frequent side effect of prostaglandins when they are administered to women as abortifacients. The fever produced by the administration of agents that enhance the synthesis of IL-1 and other cytokines, but not that caused by prostaglandins, is reduced by aspirin-like drugs (*see* Milton, 1982).

Inhibition of Prostaglandin Biosynthesis by Aspirin-like Drugs. Inhibition of prostaglandin biosynthesis by aspirin, indomethacin, or similar compounds has been demonstrated in many systems both *in vitro* and *in vivo*. This effect is dependent only on the drug reaching the cyclooxygenase enzyme. The distribution and pharmacokinetic properties of each agent thus have an important bearing on the drug's activity.

Aspirin-like drugs inhibit or interfere with a variety of other enzymes and cellular systems; however, few such actions occur at concentrations that inhibit the cyclooxygenase. It is more likely that inhibition of other enzymes may contribute to the toxic effects of these drugs, particularly with overdosage.

There is good evidence that therapeutic doses of aspirin-like compounds reduce prostaglandin biosynthesis in man. Such doses inhibit the production of prostaglandins by human platelets and reduce the prostaglandin content of human semen, urine, and the synovial fluid of arthritic knee joints. There is also a reasonably good rank–order correlation between the potency of these drugs as inhibitors of cyclooxygenase and their antiinflammatory activity (Vane and Botting, 1987). The only outstanding exception is indomethacin, which is apparently more potent in antiinflammatory tests than in the enzyme inhibition assay. In addition, there is a high degree of stereospecificity for antiinflammatory activity and inhibition of cyclooxygenase among several pairs of enantiomers of α-methyl arylacetic acids; in each instance the *d* isomer is more potent. Another example of this type of selectivity is provided by the drug sulindac; it is a prodrug that is only weakly active and is converted *in vivo* to a highly active antiinflammatory metabolite. Likewise, the drug itself has little ability to inhibit prostaglandin biosynthesis, but the sulfide metabolite is a potent inhibitor. Nevertheless, actions in addition to inhibition of cyclooxygenase may be involved in the therapeutic effects of aspirin-like drugs in the treatment of rheumatoid arthritis (*see* above). Furthermore, the degree to which microsomal preparations of cyclooxygenase from different tissues are inhibited by aspirin-like drugs varies considerably. This variability may result because there are multiple forms of the enzyme, and thus it may be possible to design drugs with greater tissue specificity.

Mode of Inhibitory Action. Aspirin-like drugs inhibit the conversion of arachidonic acid to the unstable endoperoxide intermediate, PGG_2, a reaction that is catalyzed by the cyclooxygenase (*see* Chapter 24). Individual agents have differing mechanisms for inhibition of cyclooxygenase; some are competitive inhibitors, but many exert effects that disappear only slowly. Others, most notably acetaminophen, can block the enzyme only in an environment that is low in peroxides (*e.g.*, the hypothalamus) (Marshall *et al.*, 1987). This may explain the poor antiinflammatory activity of acetaminophen, since sites of inflammation usually contain high concentrations of peroxides that are generated by leukocytes. Aspirin acetylates a serine at or near the active site of cyclooxygenase (Roth and Siok, 1978). Platelets are especially susceptible to this action because they have little or no capacity for protein biosynthesis and thus cannot regenerate the enzyme. In practical terms this means that a single dose of aspirin will inhibit the platelet cyclooxygenase for the life of the platelet (8 to 11 days); in man, a daily dose as small as 40 mg is sufficient to produce this effect. In contrast to aspirin, salicylic acid has no acetylating capacity. Nevertheless, it is as active as aspirin in reducing the synthesis of prostaglandins *in vivo*.

SHARED THERAPEUTIC ACTIVITIES AND SIDE EFFECTS OF ASPIRIN-LIKE DRUGS

All aspirin-like drugs are antipyretic, analgesic, and antiinflammatory, but there are important differences in their activities. For example, acetaminophen is antipyretic and analgesic but is only weakly antiinflammatory. The reasons for such differences are not fully understood, but differential sensitivity of enzymes in the target tissues may be important (*see* above).

When employed as analgesics, these drugs are usually effective only against pain of low-to-moderate intensity. Although their maximal effects are much lower, they lack the unwanted effects of the opioids on the central nervous system (CNS), includ-

ing respiratory depression and the development of physical dependence. Aspirin-like drugs do not change the perception of sensory modalities other than pain. Chronic postoperative pain or pain arising from inflammation is particularly well controlled by aspirin-like drugs, whereas pain arising from the hollow viscera is usually not relieved.

As antipyretics, aspirin-like drugs reduce the body temperature in febrile states. Although all such drugs are antipyretics and analgesics, some are not suitable for either routine or prolonged use because of toxicity; phenylbutazone is an example.

These drugs find their chief clinical application as antiinflammatory agents in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. In general, aspirin-like drugs provide only symptomatic relief from the pain and inflammation associated with the disease and do not arrest the progression of pathological injury to tissue during severe episodes.

In addition to sharing many therapeutic activities, aspirin-like drugs share several unwanted effects. The most common is a propensity to induce gastric or intestinal ulceration that can sometimes be accompanied by anemia from the resultant blood loss. Aspirin-like drugs vary considerably in their tendency to cause such erosions and ulcers (*see* individual sections). Gastric damage by these agents can be brought about by at least two distinct mechanisms. Although local irritation by orally administered drugs allows back diffusion of acid into the gastric mucosa and induces tissue damage, parenteral administration can also cause damage and bleeding. This appears to be correlated with inhibition of the biosynthesis of gastric prostaglandins, especially PGI_2 and PGE_2 (Isselbacher, in Symposium, 1987a, 1988a). These eicosanoids inhibit acid secretion by the stomach and promote the secretion of cytoprotective mucus in the intestine; inhibition of their synthesis may render the stomach more susceptible to damage.

Other side effects of these drugs that probably depend upon blockade of the synthesis of endogenous prostaglandins include disturbances in platelet function, the prolongation of gestation or spontaneous labor, and changes in renal function. Platelet function appears to be disturbed because aspirin-like drugs prevent the formation by the platelets of thromboxane A_2 (TXA_2), a potent aggregating agent. This accounts for the tendency of these drugs to increase the bleeding time. As mentioned, aspirin is a particularly effective inhibitor of platelet function; this "side effect" has been exploited in the prophylactic treatment of thromboembolic disorders. Prolongation of gestation by aspirin-like drugs has been demonstrated in both experimental animals and women. Prostaglandins of the E and F series are potent uterotropic agents, and their biosynthesis by the uterus increases dramatically in the hours before parturition. It is thus hypothesized that prostaglandins have a major role in the initiation and progression of labor and delivery (*see* Chapter 39).

Aspirin-like drugs have little effect on renal function in normal human subjects, presumably because the production of vasodilatory prostaglandins has only a minor role in Na^+-replete individuals. However, these drugs decrease renal blood flow and the rate of glomerular filtration in patients with congestive heart failure, hepatic cirrhosis with ascites, or chronic renal disease or in those who are hypovolemic for any reason (*see* Clive and Stoff, 1984; Pirson and van Ypersele de Strihou, 1986; Patrono and Dunn, 1987; Oates *et al.*, 1988); acute renal failure may be precipitated under these circumstances. In all of these settings renal perfusion is more dependent upon prostaglandins that cause vasodilatation and that can oppose the vasoconstrictive influences of norepinephrine and angiotensin II that result from the activation of pressor reflexes.

In addition to their hemodynamic effects in the kidney, aspirin-like drugs promote the retention of salt and water by reducing the prostaglandin-induced inhibition of both the reabsorption of chloride and the action of antidiuretic hormone. This may cause edema in some patients who are treated with an aspirin-like drug; it may also reduce the effectiveness of antihypertensive regimens (*see* Patrono and Dunn, 1987; Oates *et al.*, 1988). These drugs pro-

mote hyperkalemia by several mechanisms, including enhanced reabsorption of K^+ as a result of decreased availability of Na^+ at distal tubular sites and suppression of the prostaglandin-induced secretion of renin. The latter effect may account in part for the usefulness of aspirin-like drugs in the treatment of Bartter's syndrome, which is characterized by hypokalemia, hyperreninemia, hyperaldosteronism, juxtaglomerular hyperplasia, normotension, and resistance to the pressor effect of angiotensin II. Excessive production of renal prostaglandins may play an important part in the pathogenesis of this syndrome.

Although nephropathy is uncommonly associated with the long-term use of individual aspirin-like drugs, the abuse of analgesic mixtures has been linked to the development of renal injury, including papillary necrosis and chronic interstitial nephritis (*see* Kincaid-Smith, 1986). The injury is often insidious in onset, is usually manifest initially as reduced tubular function and concentrating ability, and may progress to irreversible renal insufficiency if misuse of analgesics continues. Females are involved more frequently than are males, and there is often a history of recurring urinary tract infection. Emotional disturbances are common, and other drugs may be abused concurrently. Despite numerous clinical observations and experimental studies in animals and man, crucial details of the problem remain unclear. Phenacetin was suggested to be the nephrotoxic component of analgesic mixtures and, therefore, was removed from these products. Although the incidence of analgesic nephropathy in some countries has subsequently declined, this has not been a universal result, especially in Australia. It is thus possible that chronic abuse of any aspirin-like drug or analgesic mixture may cause renal injury in the susceptible individual (*see* Maher, 1984). An acute interstitial nephritis can also occur as a rare complication of the use of aspirin-like drugs (Pirson and van Ypersele de Strihou, 1986).

Two other uses of aspirin-like drugs that depend upon their capacity to block prostaglandin biosynthesis also deserve mention. Prostaglandins have been implicated in the maintenance of patency of the ductus arteriosus, and indomethacin and related agents have been used in neonates to close the ductus when it has remained patent. The release of prostaglandins by the endometrium during menstruation may be a cause of severe cramps and other symptoms of primary dysmenorrhea; treatment of this condition with aspirin-like drugs has met with considerable success (*see* Shapiro, 1988).

Certain individuals display intolerance to aspirin and most aspirin-like drugs; this is manifest by symptoms that range from vasomotor rhinitis with profuse watery secretions, angioneurotic edema, generalized urticaria, and bronchial asthma to laryngeal edema and bronchoconstriction, hypotension, and shock. Although rare in children, this syndrome may occur in 20 to 25% of middle-aged patients with asthma, nasal polyps, or chronic urticaria (*see* Szczeklik, 1986; Oates *et al.*, 1988). Despite the resemblance to anaphylaxis, this reaction does not appear to be immunological in nature. Moreover, an individual who is intolerant to one aspirin-like drug may react when exposed to any of a variety of such agents, despite their chemical diversity. The underlying mechanism is unknown, but a common factor appears to be the ability of the drugs to inhibit cyclooxygenase. This has prompted the hypothesis that the reaction reflects the diversion of arachidonic acid metabolism toward the formation of increased amounts of leukotrienes and other products of lipoxygenase pathways (*see* Szczeklik, 1986; Stevenson and Lewis, 1987; Oates *et al.*, 1988). However, this view is as yet unproven and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction.

Choice of Drug to Be Prescribed. The choice of an agent as an antipyretic or analgesic is seldom a problem. It is in the field of rheumatology that the decision becomes complex (*see* Hess and Tangnijkul, 1986). The choice among aspirin-like agents for the treatment of arthritides is largely empirical. A drug may be chosen and given for a week or more; if the therapeutic effect is adequate, treatment should be continued unless toxicity occurs. Large variations are possible in the response of individuals to different aspirin-like drugs, even when they are closely allied members of the same chemical family. Thus, a patient may do well on one propionic acid derivative (such as ibuprofen) but not on another. This may indicate that these drugs share (unequally) different types of therapeutic actions. Discussion of principles of the use of aspirin-like drugs is provided in several symposia and a monograph (Symposium, 1983a, 1983b, 1984; Lewis and Furst, 1987).

All the drugs in this chapter, with the exception of the *p*-aminophenol derivatives, have a tendency to cause gastrointestinal side effects, which may range from mild dyspepsia and heartburn to ulceration of the stomach or duodenum, sometimes with fatal results. Hypersensitivity to aspirin is a contraindication to therapy with any of the drugs discussed in this chapter; administration of any one of these could provoke a life-threatening reaction reminiscent of anaphylactic shock (*see* above).

When dealing with a child, the choice of drugs is considerably restricted, and only drugs that have been extensively tested in children should be used. This commonly means that only aspirin, naproxen, or tolmetin should be prescribed. However, the association of Reye's syndrome in children with the administration of aspirin for the treatment of febrile viral illnesses precludes its use in this setting. The use of any of the aspirin-like drugs in pregnant women is generally not recommended. If such a drug must be given to a pregnant woman, low doses of aspirin are probably the safest. Although toxic doses of salicylates cause teratogenic effects in animals, there is no evidence to suggest that salicylates in moderate doses have teratogenic effects on the human fetus. In any case, aspirin should be discontinued prior to the anticipated time of parturition in order to avoid complications such as prolongation of labor, increased risk of postpartum hemorrhage, and intrauterine closure of the ductus arteriosus.

Many aspirin-like drugs bind firmly to plasma proteins and thus may displace certain other drugs from the binding sites. Such interactions can occur in patients given salicylates or phenylbutazone together with warfarin, a sulfonylurea hypoglycemic agent, or methotrexate; the dosage of such agents may require adjustment, or concurrent administration should be avoided. The problem with warfarin is accentuated because almost all of the aspirin-like drugs disturb normal platelet function.

Initially, fairly low doses of the agent chosen should be prescribed to determine the patient's reaction. When the patient has problems with sleeping because of pain or morning stiffness, a larger single dose of the drug may be given at night; as an alternative, single doses of another drug (*e.g.*, 50 to 100 mg of indomethacin) may be given to supplement existing medication without much danger of serious side effects. A week is generally long enough to determine the effect of a given drug. If the drug is effective, treatment should be continued, reducing the dose if possible and stopping it altogether if it is no longer necessary. Side effects usually appear in the first weeks of therapy. If the patient does not respond, another compound should be tried, since there is a marked variation in the response of individuals to different but closely related drugs.

For mild arthropathies, the scheme outlined above, together with rest and physical therapy, will probably be effective. However, patients with a more debilitating disease may not respond adequately. In such cases, more aggressive therapy should be initiated with aspirin or another agent. It is best to avoid continuous combination therapy with more than one aspirin-like drug; there is little evidence of extra benefit to the patient, and the incidence of side effects is generally additive.

For the seriously debilitated patient who cannot tolerate these drugs or in whom they are not adequately effective, other forms of therapy should be considered. Gold, hydroxychloroquine, and penicillamine are discussed in a separate section of this chapter. Other relevant drugs include immunosuppressive agents (Chapter 53) and glucocorticoids (Chapter 60).

A final important consideration is the cost of therapy, particularly since these agents are frequently used on a long-term basis. Generally speaking, aspirin is very inexpensive, ibuprofen has become less costly than phenylbutazone and indomethacin, and the cost of the newer drugs can be very high.

THE SALICYLATES

Despite the introduction of many new drugs, aspirin (acetylsalicylic acid) is still the most widely prescribed analgesic–antipyretic and antiinflammatory agent, and it is the standard for the comparison and evaluation of the others. Prodigious amounts of the drug are consumed in the United States; some estimates place the quantity as high as 10 to 20 thousand tons annually. The layman relies upon it as the common household analgesic; yet, because the drug is so generally available, its usefulness is often underrated. Despite the efficacy and safety of aspirin as an analgesic and antirheumatic agent, it is necessary to be aware of its role in Reye's syndrome and as a common cause of lethal drug poisoning in young children, as well as its potential for serious toxicity if used improperly.

The older literature on salicylates has been summarized by Hanzlik (1927). More recent reviews of some of the clinical pharmacology appear in several symposia (1983a, 1983c) and in a monograph (Rainsford, 1985a).

Chemistry. Salicylic acid (orthohydroxybenzoic acid) is so irritating that it can only be used externally; therefore, various derivatives of this acid have been synthesized for systemic use. These comprise two large classes, namely, esters of salicylic acid obtained by substitution in the carboxyl group and salicylate esters of organic acids in which the carboxyl group of salicylic acid is re-

tained and substitution is made in the OH group. For example, aspirin is an ester of acetic acid. In addition, there are salts of salicylic acid. The chemical relationships can be seen from the structural formulas shown in Table 26–1.

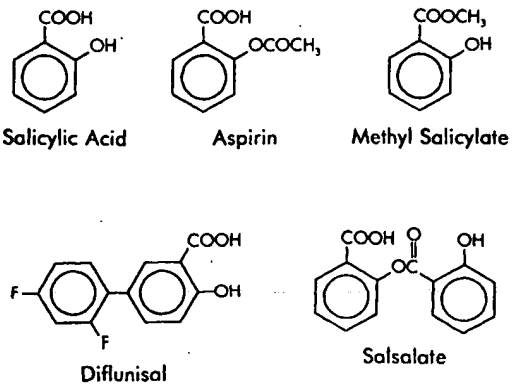
Structure–Activity Relationship. Salicylates generally act by virtue of their content of salicylic acid, although some of the unique effects of aspirin are due to its capacity to acetylate proteins (*see* below). Substitutions on the carboxyl or hydroxyl groups change the potency or toxicity of the compound. The *ortho* position of the OH group is an important feature for the action of salicylate. Benzoic acid, C_6H_5COOH, shares many of the actions of salicylic acid but is much weaker. The effects of simple substitutions on the benzene ring have been extensively studied, and new salicylate derivatives are still being synthesized. A difluorophenyl derivative, diflunisal, is also available for clinical use.

PHARMACOLOGICAL PROPERTIES

Analgesia. As noted above, the types of pain usually relieved by salicylates are those of low intensity that arise from integumental structures rather than from viscera, especially headache, myalgia, and arthralgia. The salicylates are more widely used for pain relief than is any other class of drugs. Long-term use does not lead to tolerance or addiction, and toxicity is lower than that of opioid analgesics. The salicylates alleviate pain by virtue of a peripheral action (*see* above); direct effects on the CNS may also be involved.

Antipyresis. As discussed above, salicylates usually lower elevated body temperatures rapidly and effectively. However, moderate doses that produce this effect also increase oxygen consumption and metabolic rate. In toxic doses, these compounds have a pyretic effect that results in sweating; this enhances the dehydration that occurs in salicylate intoxication (*see* below).

Table 26–1. STRUCTURAL FORMULAS OF THE SALICYLATES



Miscellaneous Neurological Effects. In high doses, salicylates have toxic effects on the CNS, consisting of stimulation (including convulsions) followed by depression. Confusion, dizziness, tinnitus, high-tone deafness, delirium, psychosis, stupor, and coma may occur. The tinnitus and hearing loss caused by salicylate poisoning are due to increased labyrinthine pressure or an effect on the hair cells of the cochlea. Tinnitus is typically observed at salicylate concentrations of 200 to 450 μg/ml, and there is a close relation between the extent of hearing loss and the concentration of salicylate in plasma. The symptoms are completely reversible within 2 or 3 days after withdrawal of the drug.

Salicylates induce nausea and vomiting, which result from stimulation of sites that are accessible from the cerebrospinal fluid (CSF), probably in the medullary chemoreceptor trigger zone (CTZ). In man, centrally induced nausea and vomiting generally appear at plasma salicylate concentrations of about 270 μg/ml, but these same effects may occur at much lower plasma values as a result of local gastric irritation.

Respiration. The effects of salicylate on respiration are important because they contribute to the serious acid–base balance disturbances that characterize poisoning by this class of compounds. Salicylates stimulate respiration directly and indirectly. Full therapeutic doses of salicylates increase oxygen consumption and CO_2 production (especially in skeletal muscle); these effects are a result of salicylate-induced uncoupling of oxidative phosphorylation (*see* below). The increased production of CO_2 stimulates respiration. The increased alveolar ventilation balances the increased CO_2 production, and thus plasma CO_2 tension (P_{CO_2}) does not change. The initial increase in alveolar ventilation is characterized mainly by an increase in depth of respiration and only a slight increase in rate. If the respiratory response to CO_2 has been depressed by the administration of a barbiturate or an opioid, salicylates will cause a marked increase in plasma P_{CO_2} and respiratory acidosis.

Salicylate directly stimulates the respira-

tory center in the medulla. This results in marked hyperventilation, characterized by an increase in depth and a pronounced increase in rate. Patients with salicylate poisoning may have prominent increases in respiratory minute volume, and respiratory alkalosis ensues. Plasma salicylate concentrations of 350 μg/ml are nearly always associated with hyperventilation in man, and marked hyperpnea occurs when the level approaches 500 μg/ml.

A depressant effect of salicylate on the medulla appears after high doses or after prolonged exposure. Toxic doses of salicylates cause central respiratory paralysis as well as circulatory collapse secondary to vasomotor depression. Since enhanced CO_2 production continues, respiratory acidosis ensues (*see* below).

Acid–Base Balance and Electrolyte Pattern. Therapeutic doses of salicylate produce definite changes in the acid–base balance and electrolyte pattern. The initial event, as discussed above, is respiratory alkalosis. Compensation for the respiratory alkalosis is achieved by increased renal excretion of bicarbonate, which is accompanied by Na^+ and K^+; plasma bicarbonate is thus lowered, and blood pH returns toward normal. This is the stage of compensated respiratory alkalosis. This stage is most often seen in adults given intensive salicylate therapy and seldom proceeds further.

Subsequent changes in acid–base status generally occur only when toxic doses of salicylates are ingested by infants and children and occasionally after large doses in adults. In infants and children, the phase of respiratory alkalosis may not be observed, since the child with salicylate intoxication is rarely seen early enough. The stage generally present is characterized by a decrease in blood pH, a low plasma bicarbonate concentration, and a normal or nearly normal plasma P_{CO_2}; except for the P_{CO_2}, these changes resemble those of metabolic acidosis. However, in reality there is a combination of respiratory acidosis and metabolic acidosis produced as follows. The enhanced production of CO_2 outstrips its alveolar excretion because of direct salicylate-induced depression of respiration; consequently, plasma P_{CO_2} increases and blood pH decreases. Since the concentration of bicarbonate in plasma is already low because of increased renal bicarbonate excretion, the acid–base status at this stage is essentially an uncompensated respiratory acidosis. Superimposed, however, is a true metabolic acidosis caused by accumulation of acids as a result of three processes. First, toxic concentrations of salicylates displace about 2 to 3 mEq per liter of plasma bicarbonate. Second, vasomotor depression caused by toxic doses of salicylate impairs renal function with consequent accumulation of strong acids of metabolic origin, namely, sulfuric and phosphoric acids. Third, organic acids accumulate secondary to salicylate-induced derangement of carbohydrate metabolism, especially pyruvic, lactic, and acetoacetic acids.

The series of events that produce acid–base disturbances in salicylate intoxication also cause alterations of water and electrolyte balance. The low plasma P_{CO_2} leads to decreased renal tubular reabsorption of bicarbonate and increased renal excretion of Na^+, K^+, and water (*see* introduction to Section VI). In addition, water is lost by salicylate-induced sweating and by insensible water loss through the lungs during hyperventilation, and dehydration rapidly occurs. Since more water than electrolyte is lost through the lungs and by sweating, the dehydration is associated with hypernatremia. Prolonged exposure to high doses of salicylate also causes depletion of K^+ due to both renal and extrarenal factors.

Cardiovascular Effects. Ordinary therapeutic doses of salicylates have no important direct cardiovascular actions. The peripheral vessels tend to dilate after large doses because of a direct effect on their smooth muscle. Toxic amounts depress the circulation directly and by central vasomotor paralysis.

In patients given large doses of sodium salicylate or aspirin, such as the doses used in acute rheumatic fever, the circulating plasma volume increases (about 20%), the hematocrit falls, and cardiac output and work are increased. Consequently, in patients with clear evidence of carditis, such alterations can cause congestive failure and pulmonary edema. High doses of salicylates can also produce noncardiogenic pulmonary edema, particularly in older patients who are ingesting salicylates regularly over a long term.

Gastrointestinal Effects. The ingestion of salicylate may result in epigastric distress, nausea, and vomiting. The mechanism of the emetic effect is discussed above. Salic-

ylate may also cause gastric ulceration; exacerbation of peptic ulcer symptoms (heartburn, dyspepsia), gastrointestinal hemorrhage, and erosive gastritis have all been reported in patients on high-dose therapy, but may occur rarely with low doses as a hypersensitivity response. Salicylate-induced gastric bleeding is painless and may lead to an iron-deficiency anemia.

The daily ingestion of 4 or 5 g of aspirin, a dose that produces plasma salicylate concentrations in the usual range for antiinflammatory therapy (120 to 350 μg/ml), results in an average fecal blood loss of about 3 to 8 ml per day as compared with approximately 0.6 ml per day in untreated subjects (Leonards and Levy, 1973). Gastroscopic or direct examination in salicylate-treated subjects reveals discrete ulcerative and hemorrhagic lesions of the gastric mucosa; in many cases, multiple hemorrhagic lesions with sharply demarcated areas of focal necrosis are observed. The incidence of bleeding is highest with salicylates that dissolve slowly and deposit as particles in the gastric mucosal folds.

As discussed above, the mechanisms by which salicylates injure gastric mucosal cells are complex (*see* Ivey, in Symposium, 1988a). Deleterious effects result from local actions (*e.g.*, "back diffusion" of acid), which cause injury to mucosal cells and the submucosal capillaries with subsequent necrosis and bleeding, and from effects secondary to inhibition of prostaglandin synthesis (*e.g.*, increased acid secretion and decreased mucus production). There may also be an increased tendency to bleed because of impaired platelet aggregation.

Hepatic and Renal Effects. Salicylates can produce at least two forms of hepatic injury. In one form, hepatotoxicity is dose dependent and is usually associated with plasma concentrations that are maintained above 150 μg/ml. The vast majority of cases occur in patients with connective tissue disorders. There are usually no symptoms, and elevated enzyme (transaminase) activities in plasma are the principal indications of hepatic damage. About 5% of the patients also have hepatomegaly, anorexia, and nausea, and jaundice may be present; in these instances, salicylates should be discontinued because of the potential hazard of fatal hepatic necrosis. For these and other reasons, restriction of salicylates has been advised in patients with chronic liver disease.

Considerable evidence implicates the use of salicylates as an important factor in the severe hepatic injury and encephalopathy observed in Reye's syndrome (*see* Heubi *et al.*, 1987; Hurwitz *et al.*, 1987; Pinsky *et al.*, 1988). This syndrome is a rare but often fatal consequence of infection with varicella and various other viruses, especially the influenza virus. Although a causal relationship between salicylates and Reye's syndrome has not been established, there is a strong epidemiological association. It has been proposed that aspirin and the viral illness may act to damage mitochondria, perhaps preferentially in genetically predisposed individuals (Heubi *et al.*, 1987; Pinsky *et al.*, 1988). The use of salicylates in children or adolescents with chickenpox or influenza is contraindicated.

As discussed above, salicylates can cause retention of salt and water as well as acute reduction of renal function in patients with congestive heart failure or hypovolemia. Although long-term use of salicylates alone is rarely associated with nephrotoxicity, the prolonged and excessive ingestion of analgesic mixtures containing salicylates in combination with acetaminophen or salicylamide can produce papillary necrosis and interstitial nephritis (Clive and Stoff, 1984).

Uricosuric Effects. The effects of salicylates on uric acid excretion are markedly dependent on dose. Low doses (1 or 2 g per day) may decrease urate excretion and elevate plasma urate concentrations; intermediate doses (2 or 3 g per day) usually do not alter urate excretion; large doses (over 5 g per day) induce uricosuria and lower plasma urate levels. Such large doses are poorly tolerated. Even small doses of salicylate can block the effects of probenecid and other uricosuric agents that decrease tubular reabsorption of uric acid (*see* Chapter 30).

Effects on the Blood. Ingestion of aspirin by normal individuals causes a definite prolongation of the bleeding time. For example, a single dose of 0.65 g of aspirin approximately doubles the mean bleeding time of normal persons for a period of 4 to 7 days. This effect is probably due to acetylation of platelet cyclooxygenase and the consequent reduced formation of TXA_2.

Patients with severe hepatic damage, hypoprothrombinemia, vitamin K deficiency, or hemophilia should avoid aspirin because the inhibition of platelet hemostasis can result in hemorrhage. If conditions

permit, aspirin therapy should be stopped at least 1 week prior to surgery; care should also be exercised in the use of aspirin during long-term treatment with oral anticoagulant agents because of the possible danger of blood loss from the gastric mucosa. However, the intentional use of aspirin is being investigated for the prophylaxis of thromboembolic disease, especially in the coronary and cerebral circulation (*see* Reilly and Fitzgerald, 1988; *see also* Chapter 55).

Salicylates do not ordinarily alter the leukocyte, platelet, or erythrocyte count, the hematocrit, or the hemoglobin content. In acute rheumatic fever, salicylate therapy can reduce leukocytosis and the elevated erythrocyte sedimentation rate. The plasma iron concentration is markedly decreased and erythrocyte survival time is shortened by doses of 3 to 4 g per day. Aspirin is included among the drugs that can cause a mild degree of hemolysis in individuals with a deficiency of glucose-6-phosphate dehydrogenase.

Effects on Rheumatic, Inflammatory, and Immunological Processes, and on Connective Tissue Metabolism. For almost 100 years the salicylates have retained their preeminent position in the treatment of the rheumatic diseases. Although they suppress the clinical signs and even improve the histological picture in acute rheumatic fever, subsequent tissue damage such as cardiac lesions and other visceral involvement is unaffected. In addition to their action on prostaglandin biosynthesis, the mechanism of action of the salicylates in rheumatic disease may also involve effects on other cellular and immunological processes in mesenchymal and connective tissues.

Because of the known relationship between rheumatic fever and immunological processes, attention has been directed to the capacity of salicylates to suppress a variety of antigen–antibody reactions. These include the inhibition of antibody production, of antigen–antibody aggregation, and of antigen-induced release of histamine. Salicylates also induce a nonspecific stabilization of capillary permeability during immunological insults. The concentrations of salicylates needed to produce these effects are high, and the relationship of these effects to the antirheumatic efficacy of salicylates is yet to be determined.

Salicylates can also influence the metabolism of connective tissue, and these effects may be involved in their antiinflammatory action. For example, salicylates can affect the composition, biosynthesis, or metabolism of connective tissue mucopolysaccharides in the ground substance that provides barriers to spread of infection and inflammation.

Metabolic Effects. The salicylates have multiple effects on metabolic processes, some of which have already been discussed. Only a few pertinent aspects will be presented here.

Oxidative Phosphorylation. The uncoupling of oxidative phosphorylation by salicylate is similar to that induced by 2,4-dinitrophenol. The effect may occur with doses of salicylate used in the treatment of rheumatoid arthritis and can result in the inhibition of a number of adenosine triphosphate (ATP)–dependent reactions. Other consequences include the salicylate-induced increase in oxygen uptake and carbon dioxide production described above, the depletion of hepatic glycogen, and the pyretic effect of toxic doses of salicylate. Salicylate in toxic doses may decrease aerobic metabolism as a result of inhibition of various dehydrogenases, by competing with the pyridine nucleotide coenzymes, and inhibition of some oxidases that require nucleotides as coenzymes, such as xanthine oxidase.

Carbohydrate Metabolism. Large doses of salicylates may cause hyperglycemia and glycosuria and deplete liver and muscle glycogen; these effects are partly explained by the release of epinephrine. Such doses also reduce aerobic metabolism of glucose, increase glucose-6-phosphatase activity, and promote the secretion of glucocorticoids.

Nitrogen Metabolism. Salicylate in toxic doses causes a significant negative nitrogen balance, characterized by an aminoaciduria. Although adrenocortical activation may contribute to the negative nitrogen balance by enhancing protein catabolism, the mechanism of the aminoaciduria produced by salicylates is poorly understood.

Fat Metabolism. Salicylates reduce lipogenesis by partially blocking incorporation of acetate into fatty acids; they also inhibit epinephrine-stimulated lipolysis in fat cells and displace long-chain fatty acids from binding sites on human plasma proteins. The combination of these effects leads to increased entry and enhanced oxidation of fatty acids in muscle, liver, and other tissues, and to decreased plasma concentrations of free fatty acids, phospholipid, and cholesterol; the oxidation of ketone bodies is also increased.

Endocrine Effects. *Adrenal Cortex.* Very large doses of salicylate stimulate steroid secretion by the adrenal cortex through an effect on the hypothalamus and transiently increase plasma concentrations of free adrenocorticosteroids by displacement from plasma proteins. However, it is clear that the antiinflammatory effects of salicylate are independent of these effects on adrenocorticosteroids.

Thyroid Gland. Long-term administration of salicylate decreases thyroidal uptake and clearance of iodine, but increases oxygen consumption and rate of disappearance of thyroxine and triiodothyronine from the circulation. These effects are probably due to the competitive displacement by

salicylate of thyroxine and triiodothyronine from transthyretin and the thyroxine-binding globulin in plasma.

Salicylates and Pregnancy. There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have significantly reduced weights at birth. In addition, there is an increase in perinatal mortality, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and complicated deliveries (*see* above).

Local Irritant Effects. Salicylic acid is quite irritating to skin and mucosa and destroys epithelial cells. The keratolytic action of the free acid is employed for the local treatment of warts, corns, fungal infections, and certain types of eczematous dermatitis. The tissue cells swell, soften, and desquamate. The salts of salicylic acid are innocuous to the unbroken skin; however, if the free acid is released in the stomach, the gastric mucosa may be irritated. Methyl salicylate (oil of wintergreen) is irritating to both skin and gastric mucosa and is only used externally.

Pharmacokinetics and Metabolism. These important aspects of the salicylates have been reviewed by Davison (1971).

Absorption. Orally ingested salicylates are absorbed rapidly, partly from the stomach but mostly from the upper small intestine. Appreciable concentrations are found in plasma in less than 30 minutes; after a single dose, a peak value is reached in about 2 hours and then gradually declines. Rate of absorption is determined by many factors, particularly the disintegration and dissolution rates if tablets are given, the pH at the mucosal surfaces, and gastric emptying time.

Salicylate absorption occurs by passive diffusion primarily of nondissociated salicylic acid or acetylsalicylic acid across gastrointestinal membranes and hence is influenced by gastric pH. Even though salicylate is more ionized as the pH is increased, a rise in pH also increases the solubility of salicylate, and the overall effect is to enhance absorption. As a result, there is little meaningful difference between the rates of absorption of sodium salicylate, aspirin, and the numerous buffered preparations of salicylates. The presence of food delays absorption of salicylates.

Rectal absorption of salicylate is usually slower, incomplete, and unreliable; rectal administration is therefore not advisable when high plasma concentrations of the drug are required. Salicylic acid is rapidly absorbed from the intact skin, especially when applied in oily liniments or ointments, and systemic poisoning has occurred from its application to large areas of skin. Methyl salicylate is likewise speedily absorbed when applied cutaneously; its gastrointestinal absorption may be delayed many hours, and, therefore, gastric lavage should be performed even in cases of poisoning that are seen late.

When nonionized salicylic acid in the gastric lumen enters mucosal cells, large amounts of salicylate can accumulate because of dissociation to the ionized species at the intracellular pH. As a result, gastric mucosal damage may occur.

Distribution. After absorption, salicylate is distributed throughout most body tissues and most transcellular fluids, primarily by pH-dependent passive processes. Salicylate is actively transported by a low-capacity, saturable system out of the CSF across the choroid plexus. The drug readily crosses the placental barrier.

The volumes of distribution of usual doses of aspirin and sodium salicylate in normal subjects average about 170 ml/kg of body weight; at high therapeutic doses, this volume increases to about 500 ml/kg because of saturation of binding sites on plasma proteins. Ingested aspirin is mainly absorbed as such, but some enters the systemic circulation as salicylic acid, because of hydrolysis by esterases in the gastrointestinal mucosa and the liver. Aspirin can be detected in the plasma only for a short time as a result of hydrolysis in plasma, liver, and erythrocytes; for example, 30 minutes after a dose of 0.65 g, only 27% of the total plasma salicylate is in the acetylated form. As a result, plasma concentrations of aspirin are always low and rarely exceed 20 μg/ml at ordinary therapeutic doses. Methyl salicylate is also rapidly hydrolyzed to salicylic acid, mainly in the liver.

At concentrations encountered clinically, from 80 to 90% of the salicylate is bound to plasma proteins, especially albumin; this fraction declines as plasma concentrations are increased. In addition, hypoalbuminemia, as may occur in rheumatoid arthritis, is associated with a proportionately higher level of free salicylate in the plasma. Salicylate competes with a variety of compounds for plasma protein binding sites; these include thyroxine, triiodothyronine, penicillin, phenytoin, sulfinpyrazone, bilirubin, uric acid, and naproxen. Aspirin is bound to a more limited extent; however, it acetylates human plasma albumin *in vivo* by reaction with the ϵ-amino group of lysine; this acetylation may change the binding of drugs to albumin. Hormones, DNA, platelets, and hemoglobin and other proteins are also acetylated.

Biotransformation and Excretion. The biotransformation of salicylate takes place in many tissues, but particularly in the hepatic endoplasmic reticulum and mitochondria. The three chief metabolic products are

salicyluric acid (the glycine conjugate), the ether or phenolic glucuronide, and the ester or acyl glucuronide. In addition, a small fraction is oxidized to gentisic acid (2,5-dihydroxybenzoic acid) and to 2,3-dihydroxybenzoic and 2,3,5-trihydroxybenzoic acids; gentisuric acid, the glycine conjugate of gentisic acid, is also formed.

Salicylates are excreted in the urine as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides, and gentisic acid (<1%). However, excretion of free salicylate is extremely variable and depends upon both the dose and the urinary pH. In alkaline urine, more than 30% of the ingested drug may be eliminated as free salicylate, whereas in acidic urine this may be as low as 2%.

The plasma half-life for aspirin is approximately 15 minutes; that for salicylate is 2 to 3 hours in low doses and about 12 hours at usual antiinflammatory doses. The half-life of salicylate may be as long as 15 to 30 hours at high therapeutic doses or when there is intoxication. This dose-dependent elimination is the result of the limited ability of the liver to form salicyluric acid and the phenolic glucuronide, and a larger proportion of unchanged drug is excreted in the urine at higher doses.

The plasma concentration of salicylate is increased by conditions that decrease glomerular filtration rate or reduce its secretion by the proximal tubule, such as renal disease or the presence of inhibitors that compete for the transport system (*e.g.*, probenecid). Changes in urinary pH also have significant effects on salicylate excretion; for example, the clearance of salicylate is about four times as great at pH 8.0 as at pH 6.0, and it is well above the glomerular filtration rate at pH 8.0. High rates of urine flow decrease tubular reabsorption, whereas the opposite is true in oliguria. The conjugates of salicylic acid with glycine and glucuronic acid do not readily back diffuse across the renal tubular cells. Their excretion, therefore, is both by glomerular filtration and proximal tubular secretion and is not pH dependent.

Preparations, Routes of Administration, and Dosage. The two most commonly used preparations of salicylate for systemic effects are sodium salicylate and aspirin (acetylsalicylic acid).

Sodium salicylate is available in regular or enteric-coated tablets that contain 325 or 650 mg of drug and in an injectable solution for parenteral use. *Aspirin* is available in regular or enteric-coated tablets ranging from 65 to 975 mg and in suppositories; timed-release tablets are also marketed.

The dose of salicylate depends on the condition being treated. The usual single dose of aspirin in adults is 300 mg to 1.0 g. This may be repeated every 4 hours. More intensive dosage regimens are employed in acute rheumatic fever and rheumatoid arthritis (*see* below).

The route of administration is nearly always oral. Parenteral administration is rarely necessary. The rectal administration of aspirin suppositories may be necessary in infants or when oral medication is not retained. Salicylates are conveniently taken in tablets or capsules with a full glass of water to minimize gastric irritation. Aspirin is poorly soluble, has many chemical incompatibilities, and should be dispensed only in solid dry form. Timed-release preparations are of limited value, since the half-time for elimination of salicylate is so long, particularly during high-dose therapy. Absorption from enteric-coated tablets is sometimes incomplete, but these formulations may produce less gastrointestinal irritation. Preparations of aspirin containing alkali or buffer are sometimes better tolerated, but alkalinization of the urine, which may occur, can shorten the plasma half-life of salicylates considerably (*see* above).

Other salicylates that are available for systemic use include *salsalate* (salicylsalicylic acid; DICALCID); it is hydrolyzed to salicylic acid during and after absorption. The drug is available in 500- and 750-mg tablets and 500-mg capsules; the maximal daily dose is 3 g given in 2 to 4 divided doses. *Salicylamide*, which is not metabolized to salicylate *in vivo*, has antipyretic, analgesic, and antiinflammatory effects similar to those of salicylate. It remains available only in certain combination preparations. Sodium thiosalicylate (injection), choline salicylate (oral liquid), and magnesium salicylate (tablets) are also available. A combination of choline and magnesium salicylates (TRILISATE) is formulated to contain 500 mg of salicylate per 5 ml (oral liquid) or 500 to 1000 mg per tablet; 1 to 3 doses per day may be given. The nonacetylated salicylates appear to produce a lower incidence of gastrointestinal ulceration and have less effect on platelet aggregation than does aspirin. Diflunisal is discussed below.

Mesalamine (5-aminosalicylic acid) is a salicylate that is used for its local effects in the treatment of inflammatory bowel disease. The drug is not effective orally because it is poorly absorbed and is inactivated before reaching the lower intestine. It is currently available as a rectal suspension enema (ROWASA) for treatment of mild-to-moderate proctosigmoiditis; formulations that deliver the intact drug to the lower intestine are under investigation (Schroeder *et al.*, 1987). *Sulfasalazine* (salicylazosulfapyridine; AZULFIDINE, AZALINE) contains mesalamine linked covalently to sulfapyridine (*see* Chapter 45); it is poorly absorbed after oral administration, but it is cleaved to its active components by bacteria in the colon. The drug is of benefit in the treatment of inflammatory bowel disease, principally because of the local actions of mesalamine. Sulfasalazine has also been used in

the treatment of rheumatoid arthritis and ankylosing spondylitis (*see* Symposium, 1986a, 1988b); sulfapyridine, which is absorbed systemically, appears to be the most important therapeutic component in these conditions.

Methyl salicylate (sweet birch oil, wintergreen oil, gaultheria oil, betula oil) is employed only for cutaneous counterirritation and is distributed in the form of salves, liniments, and other preparations. *Salicylic acid* is primarily used for local application as a keratolytic agent in plasters, liquids, creams, ointments, and other topical preparations. However, a transdermal patch containing 15% salicylic acid has recently been marketed for systemic therapy.

TOXIC EFFECTS

As a result of their wide use and ready availability, salicylates are frequently the cause of intoxication. Poisoning or serious intoxication often occurs in children and is sometimes fatal. The drug should not be viewed as a harmless household remedy.

Hypersensitivity is also a cause of untoward responses to salicylate. Furthermore, renal or hepatic insufficiency or hypoprothrombinemia or other bleeding disorders enhance the possibility of salicylate toxicity. Children with fever and dehydration are particularly prone to intoxication from relatively small doses of salicylate. In addition, the use of aspirin is contraindicated in children and adolescents with febrile viral illnesses because of the risk of Reye's syndrome. Many of the unwanted effects that are common to the aspirin-like drugs are discussed above.

Salicylate Intoxication. The fatal dose varies with the preparation of salicylate. From 10 to 30 g of sodium salicylate or aspirin has caused death in adults, but much larger amounts (130 g of aspirin, in one case) have been ingested without fatal outcome. The lethal dose of methyl salicylate is considerably less than that of sodium salicylate. As little as 4 ml (4.7 g) of methyl salicylate may be fatal in children.

Symptoms and Signs. Mild chronic salicylate intoxication is termed salicylism. When fully developed, the syndrome includes headache, dizziness, ringing in the ears, difficulty in hearing, dimness of vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, and occasionally diarrhea. A more severe degree of salicylate intoxication is characterized by more pronounced CNS disturbances (including generalized convulsions and coma), skin eruptions, and marked alterations in acid–base balance. Fever is usually prominent, especially in children. Dehydration often occurs as a result of hyperpyrexia, sweating, vomiting, and the loss of water vapor during hyperventilation. Gastrointestinal symptoms are often present; about 50% of individuals with plasma salicylate concentrations of more than 300 μg/ml experience nausea.

A prominent feature of salicylate intoxication is the disturbance in acid–base balance and electrolyte composition of the plasma described above. The most severe metabolic disturbances occur in infants and very young children who become intoxicated as the result of therapeutic overdosage; most of the acidotic patients seen with salicylate intoxication are in this group.

Hemorrhagic phenomena are occasionally seen during salicylate poisoning, the mechanism and significance of which have been discussed. Petechial hemorrhages are a prominent postmortem feature. Thrombocytopenic purpura is a rare complication. While hyperglycemia may occur during salicylate intoxication, hypoglycemia may be a serious consequence of toxicity in young children. It should be seriously considered in any young child with coma, convulsions, or cardiovascular collapse.

Severe toxic encephalopathy may be a prominent feature of salicylate poisoning and may be difficult to differentiate from rheumatic encephalopathy. As poisoning progresses, central stimulation is replaced by increasing depression, stupor, and coma. Cardiovascular collapse and respiratory insufficiency ensue, and terminal asphyxial convulsions and pulmonary edema sometimes appear. Death usually results from respiratory failure after a period of unconsciousness.

Salicylate toxicity in adults may not be readily diagnosed because such patients usually become intoxicated from their therapeutic regimen; there is no history of acute overdosage. Prominent features of toxicity in this group are noncardiogenic pulmonary edema, nonfocal neurological abnormalities, and laboratory findings that include acid–base abnormalities, unexplained ketosis, and a prolonged prothrombin time (Anderson *et al.*, 1976).

Symptoms of poisoning by methyl salicylate differ little from those described for aspirin. Central excitation, intense hyperpnea, and hyperpyrexia are prominent features. The odor of the drug can easily be detected on the breath and in the urine and vomitus. Poisoning by salicylic acid differs only in the increased prominence of gastrointestinal symptoms due to the marked local irritation.

Treatment. Salicylate poisoning represents an acute medical emergency, and death may result despite all recommended procedures. The treatment is largely symptomatic. Salicylate medication is withdrawn as soon as intoxication is suspected. The patient should be hospitalized, particularly in cases of poisoning with methyl salicylate. Blood should be obtained for plasma salicylate determinations and acid–base and electrolyte studies. The salicylate concentration is reasonably well correlated with clinical severity, when corrected for the duration of the intoxication, and is of value in assessing the type of therapy to be instituted. Since absorption of salicylate from the gastrointestinal tract may be delayed for many hours after an overdose, measures to reduce such absorption should

always be employed. These include induction of emesis, gastric lavage, administration of activated charcoal, or a combination of these.

Hyperthermia and dehydration are the immediate threats to life, and the initial therapy must be directed to their correction and to the maintenance of adequate renal function. External sponging with tepid water or alcohol should be provided quickly to any child with very high fever. Adequate amounts of intravenous fluids must be given promptly. The type and amount of solutions to be employed depend upon the interpretation of the laboratory data on acid–base balance. If the patient presents with an acidosis, correction of the low blood pH is essential, especially since acidosis results in a shift of salicylate from plasma into brain and other tissues. Bicarbonate solution should be infused intravenously, if possible, in sufficient quantity to maintain alkaline diuresis. Correction of ketosis and hypoglycemia by administration of glucose is also essential for complete control of the metabolic acidosis; however, the ketosis clears only slowly. If K^+ deficiency occurs during salicylate intoxication, it should be treated by adding the cation to the intravenous fluids once it has been determined that urine formation is adequate. Plasma transfusion may be beneficial, especially if the shock syndrome intervenes. Hemorrhagic phenomena may necessitate whole-blood transfusion and vitamin K (phytonadione).

Measures to rid the body of salicylate rapidly should be undertaken immediately. Forced diuresis with alkalinizing solution appears to be better than alkali alone; however, this may be dangerous in adults who are prone to develop pulmonary edema. In severe intoxication, hemodialysis is the most effective measure available for the removal of salicylate and for the correction of the electrolyte and acid–base disturbances. Hemodialysis should be considered in patients with salicylate concentrations above 1000 μg/ml, in those with severe acid–base disturbances whose clinical condition is deteriorating despite otherwise-appropriate therapy, and in those who have associated serious disease, particularly cardiac, pulmonary, or renal disease. (*See* Brenner and Simon, 1982; Meredith and Vale, 1986.)

Aspirin Hypersensitivity. Aspirin hypersensitivity or intolerance is discussed above. It is important to recognize this syndrome even though it is rather uncommon, since the administration of aspirin and many other aspirin-like drugs may result in severe and possibly fatal reactions. The nonacetylated salicylates appear to be considerably less apt to produce these reactions as compared with aspirin and other agents. Treatment of such responses does not differ from that ordinarily employed in acute anaphylactic reactions. Epinephrine is the drug of choice and usually controls angioedema and urticaria without difficulty.

THERAPEUTIC USES

There are many systemic and a few local uses of the salicylates. Several are based on tradition and empirical results rather than on a clear understanding of the mechanism of therapeutic benefit.

Systemic Uses. *Antipyresis.* Antipyretic therapy is reserved for patients in whom fever in itself may be deleterious, and for those who experience considerable relief when a fever is lowered. Little is known about the relationship between fever and the acceleration of inflammatory or immune processes; it may at times be a protective physiological mechanism. The course of the patient's illness may be obscured by the relief of symptoms and the reduction of fever from the use of antipyretic drugs. The antipyretic dose of salicylate for adults is 325 to 650 mg orally every 4 hours; for children, 50 to 75 mg/kg per day is given in four to six divided doses, not to exceed a total daily dose of 3.6 g.

Analgesia. Salicylate is valuable for the nonspecific relief of certain types of pain, for example, headache, arthritis, dysmenorrhea, neuralgia, and myalgia. For this purpose, it is prescribed in the same doses and manner as for antipyresis.

Acute Rheumatic Fever. In this disease, the salicylates suppress the acute exudative inflammatory process but do not affect the duration or progression of the disease or the later phases of granulomatous inflammation or scar formation. Nevertheless, if a patient has severe carditis and heart failure, the nonspecific antiinflammatory effect of salicylates and particularly of adrenocorticosteroids may be invaluable in reducing the burden upon the heart.

For maximal suppression of rheumatic inflammation, doses that provide a plasma salicylate concentration of 150 to 300 μg/ml should be maintained, but polyarthritis and fever usually respond to smaller amounts. For adults, a total daily dosage of 5 to 8 g, given at intervals in 1-g amounts, usually suffices. Children are given 100 mg/kg per day, in divided portions every 4 to 6 hours, for up to 1 week; the dose is then reduced in stepwise fashion at weekly intervals to 60 to 75 mg/kg per day and maintained as long as necessary. Anorexia, tinnitus, nausea, and vomiting are common during the first 3 or 4 days of therapy, but tend to subside despite continuation of medication. Ordinarily, full doses are continued until at least 2 weeks after the patient is asymptomatic and all evidence of active inflammation has disappeared. The drug is then gradually discontinued over a period of 7 to 10 days. If symptoms and signs of the disease reappear, salicylate therapy is reinstituted. Therapy with glucocorticoids does not yield overall results superior to those obtained with the salicylates; salicylate and glucocorticoids are additive in their effects. If carditis is not evident, salicylates and not steroids should be used. However, if acute severe carditis is present, most investigators believe adrenocorticosteroids should be given instead of salicylates, at least initially.

Rheumatoid Arthritis. Despite the development of the newer antiinflammatory agents, salicylates are still regarded as the standard with which other drugs should be compared for the treatment of

rheumatoid arthritis. In addition to the analgesia that allows more effective therapeutic exercises, there is improvement in appetite and a feeling of well-being. Salicylates also reduce the inflammation in joint tissues and surrounding structures. Damage to joints is the most difficult aspect of rheumatoid arthritis to manage, and any agent that reduces the inflammation is important in lessening or delaying the development of crippling. Salicylates can be shown to produce objectively measurable antiinflammatory changes when given in large doses for long periods to patients with active rheumatoid disease. Large doses of salicylates, such as those used for rheumatic fever (4 to 6 g daily), are advised, but some patients respond well to less.

The majority of patients with rheumatoid arthritis can be controlled with salicylates alone or with other aspirin-like antiinflammatory agents. Some require therapy with more toxic drugs, such as gold salts, hydroxychloroquine, penicillamine, adrenocorticosteroids, or immunosuppressive agents.

Other Uses. Because of the potent and long-lasting effect of low doses of aspirin on platelet function, this drug is used in the treatment or prophylaxis of diseases associated with platelet hyperaggregability, such as coronary artery disease and postoperative deep-vein thrombosis (*see* Chapter 55). The effectiveness of such therapy appears to depend upon blockade of TXA_2 synthesis by platelets without preventing production of PGI_2 by endothelial cells (*see* Chapters 24 and 55). Although the optimal dosage has not been established, the frequency of beneficial effects appear to be greater when the dose of aspirin is 325 mg per day or lower. In the largest study to date, the ingestion of 325 mg of aspirin every other day reduced the incidence of myocardial infarction in male physicians by more than 40%; no effect was detected on the incidence of stroke (Steering Committee of the Physicians' Health Study Research Group, 1989).

A relative excess of TXA_2 over PGI_2 has been implicated in the genesis of preeclampsia and hypertension induced by pregnancy (*see* Lubbe, 1987). The administration of 60 or 100 mg of aspirin per day to pregnant women who have a high risk of developing hypertension reduces the formation of thromboxane A_2 without changing the production of PGI_2 and may lower the incidence of preeclampsia (Benigni *et al.*, 1989; Schiff *et al.*, 1989).

Relationship of Plasma Salicylate Concentration to Therapeutic Effect and Toxicity. For optimal antiinflammatory effect for patients with rheumatic diseases, plasma salicylate concentrations of 150 to 300 μg/ml are required. In this range, the clearance of the drug is nearly constant (despite the fact that saturation of metabolic capacity is approached) because the fraction of drug that is free and thus available for metabolism or excretion increases as binding sites on plasma proteins are saturated. The total concentration of salicylate in plasma is thus a relatively linear function of dose. It is important to individualize the total dose of aspirin, especially because the range of plasma salicylate concentrations needed for optimal antiinflammatory effects may overlap that at which tinnitus is noted. Tinnitus may be a reliable index of therapeutic plasma concentration in patients with normal hearing, but obviously not in those with a preexisting hearing loss. Hyperventilation generally occurs at concentrations greater than 350 μg/ml, and other signs of intoxication, such as acidosis, at concentrations greater than 460 μg/ml. Single analgesic–antipyretic doses of salicylate usually yield plasma concentrations below 60 μg/ml.

The plasma concentration of salicylate is generally little affected by other drugs, but concurrent administration of aspirin lowers the concentrations of indomethacin, naproxen, and fenoprofen, at least in part by displacement from plasma proteins. Important adverse interactions of aspirin with warfarin and methotrexate are mentioned above. Other interactions of aspirin include the antagonism of spironolactone-induced natriuresis and the blockade of the active transport of penicillin from CSF to blood.

Local Uses. Salicylic acid is applied topically as a keratolytic agent. In combination with benzoic acid, it is often prescribed for epidermophytosis. Salicylic acid is also employed as a wart and corn remover (10 to 20% in collodion).

Methyl salicylate is reserved for external use as a counterirritant. It is employed for painful muscles or joints and distributed in an ointment, liniment, or other preparation. Absorption of methyl salicylate can occur through the skin, and death has resulted from systemic poisoning from the local misapplication of the drug. It is a common pediatric poison, and its use should be strongly discouraged. It is also used as a flavoring agent.

DIFLUNISAL

Diflunisal is a difluorophenyl derivative of salicylic acid (*see* Table 26–1); it is not converted to salicylic acid *in vivo*. Diflunisal is more potent than aspirin in antiinflammatory tests in animals and appears to be a competitive inhibitor of cyclooxygenase. However, it is largely devoid of antipyretic effects, perhaps because of poor penetration into the CNS. The drug has been used primarily as an analgesic in the treatment of osteoarthritis and musculoskeletal strains or sprains; in these circumstances it is about three to four times more potent than aspirin. Diflunisal does not produce auditory side effects and appears to cause fewer and less intense gastrointestinal and antiplatelet effects than does aspirin.

Diflunisal is almost completely absorbed after oral administration, and peak concentrations occur in plasma within 2 to 3 hours. It is extensively bound to plasma albumin (99%). Diflunisal appears in the milk of lactating women; its penetration into the CNS is uncertain. About 90% of the drug is excreted as glucuronides, and its rate of elimination is dependent upon dosage. At the usual analgesic dose (500 to 750 mg per day) the plasma half-life ranges between 8 and 12 hours. (For reviews, *see* Brogden *et al.*, 1980; Davies, 1983; van Winzum *et al.*, in Symposium, 1983a.)

Diflunisal (DOLOBID) is marketed in 250- and 500-mg tablets. For mild-to-moderate pain, the

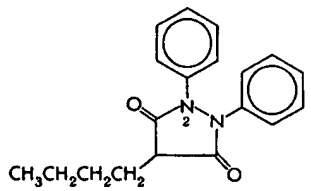
usual initial dose is 500 to 1000 mg, followed by 250 to 500 mg every 8 to 12 hours. For rheumatoid arthritis or osteoarthritis, 250 to 500 mg is administered twice daily; maintenance dosage should not exceed 1.5 g per day.

PYRAZOLON DERIVATIVES

This group of drugs includes phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone, and a more recent addition, apazone (azapropazone). With the exception of apazone, these drugs have been in clinical use for many years; although not a first-line drug, phenylbutazone is the most important from the therapeutic viewpoint, while antipyrine, dipyrone, and aminopyrine are seldom used today. Apazone is not yet available in the United States.

PHENYLBUTAZONE

Phenylbutazone was introduced in 1949 for the treatment of rheumatoid arthritis and allied disorders. Although it is an effective antiinflammatory agent, serious toxicity limits its use in long-term therapy. Its structural formula is as follows:



Phenylbutazone

Pharmacological Properties. The antiinflammatory effects of phenylbutazone are similar to those of the salicylates, but its toxicity differs significantly. Like aminopyrine, phenylbutazone can cause agranulocytosis. The pharmacology and toxicology of phenylbutazone and its metabolites and congeners have been reviewed in a symposium (Symposium, 1983a) and by Schuster and associates (Rainsford, 1985a).

Antiinflammatory Effects. Phenylbutazone has prominent antiinflammatory effects, and its frequent use to enhance the performance of race horses is well known. Somewhat similar effects are demonstrable in patients with rheumatoid arthritis and related disorders.

Antipyretic and Analgesic Effects. The antipyretic effect of phenylbutazone has been little studied in man. For pain of nonrheumatic origin, its analgesic efficacy is inferior to that of salicylates. Because of its toxicity, phenylbutazone should not be used routinely as an analgesic or antipyretic.

Uricosuric Effect. In doses of about 600 mg per day, phenylbutazone has a mild uricosuric effect, probably attributable to one of its metabolites that decreases tubular reabsorption of uric acid. Low concentrations of the drug inhibit tubular secretion of uric acid and cause retention of urate. A congener, sulfinpyrazone, is a much more effective uricosuric agent and is useful for the treatment of chronic gout (*see* below and Chapter 30).

Effects on Water and Electrolytes. Phenylbutazone causes significant retention of Na^+ and chloride, accompanied by a reduction in urine volume; edema may result. The excretion of K^+ is not changed. Plasma volume frequently increases by as much as 50%, and, as a result, cardiac decompensation and acute pulmonary edema have occurred in patients given the drug.

Other Effects. Phenylbutazone reduces the uptake of iodine by the thyroid gland, apparently secondary to inhibition of biosynthesis of organic iodine compounds. Goiter and myxedema may occasionally result from this effect.

Pharmacokinetics and Metabolism. Phenylbutazone is rapidly and completely absorbed from the gastrointestinal tract or the rectum, and the peak concentration in plasma is reached in 2 hours. After therapeutic doses, more than 98% of phenylbutazone is bound to plasma proteins. The half-life of phenylbutazone in plasma is very long—50 to 65 hours. The drug penetrates into the synovial spaces and reaches a concentration about one half of that in the plasma; significant concentrations may persist in the joints for up to 3 weeks after treatment is discontinued.

Phenylbutazone undergoes extensive metabolic transformation in man. The most significant primary reactions involve glucuronidation and hydroxylation of the phenyl rings or the butyl side chain. The conjugates are excreted in the urine and represent the bulk of the excreted drug. Oxyphenbutazone, a metabolite of phenylbutazone, has antirheumatic and Na^+-retaining activities similar to those of the parent drug. Oxyphenbutazone is also extensively bound to plasma proteins and has a half-life in plasma of several days. It accumulates significantly during long-term administration of phenylbutazone and contributes to the pharmacological and toxic effects of the parent drug. Only a trace of unchanged phenylbutazone is excreted in the urine. Oxyphenbutazone is excreted mainly as the O-glucuronide.

Drug Interactions. Other antiinflammatory agents, oral anticoagulant drugs, oral hypoglycemics, sulfonamides, and other drugs may be displaced from binding to plasma proteins by phenylbutazone. The net result depends upon the drug and its disposition after being displaced. The well-documented increased risk of bleeding associated

with concurrent phenylbutazone–warfarin medication in part involves such displacement; more importantly, phenylbutazone also reduces the clearance of the more active stereoisomer of warfarin. Displacement of plasma protein–bound thyroid hormone complicates the interpretation of thyroid function tests.

Phenylbutazone may cause induction of hepatic microsomal enzymes, and it may also inhibit inactivation of other drugs that are hydroxylated by the microsomal system. It has been said to increase the effect of insulin.

Toxic Effects. Phenylbutazone is poorly tolerated by many patients. Some type of side effect is noted in 10 to 45% of patients, and medication may have to be discontinued in 10 to 15%. Nausea, vomiting, epigastric discomfort, and skin rashes are the most frequently reported untoward effects. Diarrhea, vertigo, insomnia, euphoria, nervousness, hematuria, and blurred vision have also been observed. In addition, water and electrolyte retention and edema formation occur.

More serious forms of adverse effects include peptic ulcer (or its reactivation) with hemorrhage or perforation, hypersensitivity reactions of the serum-sickness type, ulcerative stomatitis, hepatitis, nephritis, aplastic anemia, leukopenia, agranulocytosis, and thrombocytopenia. A number of deaths have occurred, especially from aplastic anemia and agranulocytosis.

When phenylbutazone is given, the patient should be closely supervised and his blood should be examined frequently; weight should also be checked to warn of undue retention of Na^+. The drug should be given only for short periods (not more than 1 week). Even then, the incidence of disturbing side effects is about 10%. The patient must be told to discontinue the drug and promptly report to the physician if he develops fever, sore throat or other oral lesions, skin rash, pruritus, jaundice, weight gain, or tarry stools. The drug is contraindicated in patients with hypertension; cardiac, renal, or hepatic dysfunction; or a history of peptic ulcer, blood dyscrasia, or hypersensitivity to the drug. The toxic effects of the drug are more severe in elderly persons, and its use in this group is inadvisable; its use in children under the age of 14 is also not recommended.

Preparations, Route of Administration, and Dosage. *Phenylbutazone* (BUTAZOLIDIN) is available in 100-mg coated tablets and capsules for oral administration. Daily doses of 300 to 600 mg for brief periods provide maximal therapeutic effects (higher doses only increase toxicity), but the disease may subsequently be adequately controlled by doses as low as 100 to 200 mg per day. The drug should be taken with meals to lessen gastric irritation.

Therapeutic Uses. At the present time, phenylbutazone is not considered to be the drug of choice for any condition, although it is still occasionally used for the treatment of acute gout and for rheumatoid arthritis and allied disorders. Phenylbutazone should be employed only after other drugs have failed and then only after careful consideration of the risks involved as compared with the advantage to the patient. Moreover, phenylbutazone should only be used for acute exacerbations of gout or rheumatoid arthritis and not for long-term treatment. Indiscriminate use of phenylbutazone in the therapy of trivial acute or chronic musculoskeletal disorders can only be condemned.

Phenylbutazone is an alternative to colchicine in acute gout; however, other antiinflammatory agents that have a lower incidence of side effects are generally preferred. Dosage recommendations have varied, but most often an initial dose of 400 mg is given, followed by 100 mg every 4 hours for no more than 1 week, or less if articular inflammation subsides. The drug should not be used prophylactically nor as a uricosuric agent.

Phenylbutazone has a limited role for relief of acute exacerbations of rheumatoid arthritis that are not relieved by any other measures. Synovitis is often reduced by a brief regimen (300 to 600 mg on the first day, followed by no more than 400 mg daily for 3 to 7 days). Because of the high incidence of adverse effects, long-term therapy is not recommended. Brief courses of the drug, if justified, may be of similar benefit for acute exacerbations of ankylosing spondylitis and osteoarthritis.

OXYPHENBUTAZONE

Oxyphenbutazone is a *p*-hydroxy analog of phenylbutazone (on the N-1 phenyl group) and one of the active metabolites of the parent drug. Various aspects of its pharmacology and metabolism are discussed above, in comparison with phenylbutazone. Oxyphenbutazone has the same spectrum of activity, therapeutic uses, interactions, and toxicity as the parent compound, and it shares the same indications, dangers, and contraindications for clinical use. Oxyphenbutazone is said to cause somewhat less gastric irritation.

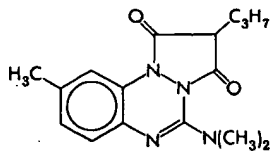
Oxyphenbutazone is marketed in 100-mg tablets. It should be taken in three or four divided portions with meals to lessen gastric irritation. Dosage of oxyphenbutazone is the same as that of phenylbutazone.

ANTIPYRINE AND AMINOPYRINE

Antipyrine (phenazone) and aminopyrine (amidopyrine) were introduced into medicine in the late nineteenth century as antipyretics and subsequently were also widely used as analgesics and antiinflammatory agents. However, clinical use of aminopyrine was sharply curtailed after its potentially fatal bone-marrow toxicity, agranulocytosis, was recognized, and antipyrine has also lost favor. Both drugs have disappeared from the therapeutic scene in the United States, but antipyrine is still employed in some countries, usually in analgesic mixtures. A variety of related pyrazolon derivatives has also enjoyed sporadic popularity, for example, dipyrone. It, too, can cause agranulocytosis. A full description of the pharmacological properties of these drugs may be found in *earlier editions* of this textbook.

APAZONE (AZAPROPAZONE)

Apazone is a pyrazolon, aspirin-like agent with a spectrum of activity very similar to that of phenylbutazone, although it is much less toxic. Thus, it is antiinflammatory, analgesic, and antipyretic. In addition, apazone is a potent uricosuric agent and is particularly useful for the treatment of acute gout. The drug is not currently available in the United States. The structural formula of apazone is as follows:



Apazone

Apazone is rapidly and probably almost completely absorbed from the gastrointestinal tract after oral administration to man; peak concentrations in plasma are achieved 4 hours later. The compound is extensively bound to plasma proteins (>95%), and the biological half-life is about 20 to 24 hours. The drug penetrates slowly into the synovial fluid. Most of the drug (about 65%) is excreted in the urine unchanged; approximately 20% is present as the 6-hydroxy derivative. There may be significant enterohepatic cycling.

Clinical experience to date suggests that apazone is generally well tolerated. Mild gastrointestinal side effects (nausea, epigastric pain, dyspepsia) occur in about 3% of patients. Skin rashes are also observed in 3% of patients, while CNS effects (headache, vertigo) are reported less frequently. The overall incidence of untoward reactions is probably 6 to 10%.

Because apazone is an inhibitor of cyclooxygenase, all precautions discussed above for the group are applicable. It should not be given to patients who have experienced aspirin-induced bronchospasm. Since the drug binds extensively to albumin, its adverse interactions with other agents may resemble those of phenylbutazone. There is no evidence that apazone causes agranulocytosis.

Apazone has been advocated for the treatment of rheumatoid arthritis, osteoarthritis, and gout. The usual dose is 1200 mg per day (in divided doses), but this may be reduced to 900 mg for maintenance therapy; elderly patients should receive lower doses. For the treatment of acute gout, an initial dose of 2400 mg (in four portions) is given on the first day, followed by daily doses of 1800 mg until the acute attack has subsided; daily maintenance doses of 1200 mg are then administered until symptoms disappear. (For a review, *see* Walker, in Rainsford, 1985b.)

PARA-AMINOPHENOL DERIVATIVES

The so-called coal tar analgesics, phenacetin and its active metabolite acetaminophen, are effective alternatives to aspirin as analgesic–antipyretic agents; however, unlike aspirin, their antiinflammatory activity is weak and seldom clinically useful. Acetaminophen has less overall toxicity and is thus preferred to phenacetin.

Because acetaminophen is well tolerated, lacks many of the side effects of aspirin, and is available without prescription, it has earned a prominent place as a common household analgesic. However, acute overdosage causes fatal hepatic damage, and the number of self-poisonings and suicides with acetaminophen has grown alarmingly in recent years. In addition, many individuals, physicians included, seem unaware of the poor antiinflammatory activity of acetaminophen.

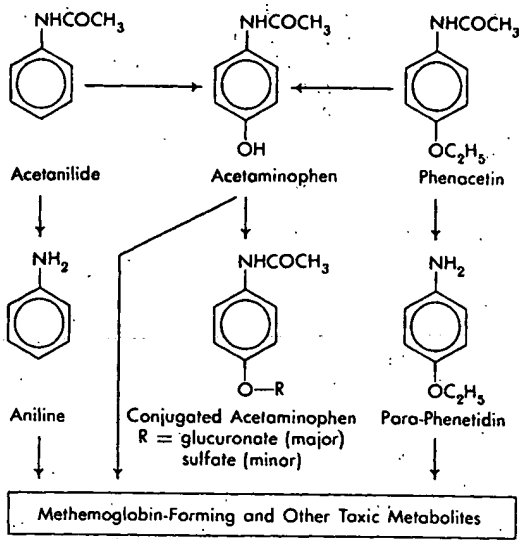
History. Acetanilide is the parent member of this group of drugs. It was introduced into medicine in 1886 under the name of antifebrin by Cahn and Hepp, who had accidentally discovered its antipyretic action. However, acetanilide proved to be excessively toxic. In the search for less toxic compounds, para-aminophenol was tried in the belief that the body oxidized acetanilide to this compound. Toxicity was not lessened, however, and a number of chemical derivatives of para-aminophenol were then tested. One of the more satisfactory of these was phenacetin (acetophenetidin). It was introduced into therapy in 1887 and was extensively employed in analgesic mixtures until it was implicated in analgesic-abuse nephropathy (*see* above).

Acetaminophen (paracetamol; N-acetyl-*p*-aminophenol) was first used in medicine by von Mering in 1893. However, it has gained popularity only since 1949, after it was recognized as the major active metabolite of both acetanilide and phenacetin.

Chemistry. The relationship between the drugs of this group and their metabolites is shown in Table 26–2. The antipyretic activity of the compounds resides in the aminobenzene structure. Introduction of other radicals into the hydroxyl group of para-aminophenol and into the free amino group of aniline reduces toxicity without loss of antipyretic action. Best results are obtained with phenolic alkyl ethers (*e.g.*, phenacetin) and with the amides (*e.g.*, acetaminophen, phenacetin).

Pharmacological Properties. Acetaminophen and phenacetin have analgesic and antipyretic effects that do not differ significantly from those of aspirin. However, as mentioned, they have only weak antiinflammatory effects. Minor metabolites contribute significantly to the toxic effects

Table 26–2. STRUCTURAL FORMULAS OF MAJOR PARA-AMINOPHENOL DERIVATIVES, AND THEIR INTERRELATIONS



of both drugs. The pharmacological properties of acetaminophen have been reviewed by Clissold (1986).

Exactly why acetaminophen is an effective analgesic–antipyretic but only a weak antiinflammatory agent has not been satisfactorily explained. An antiinflammatory effect can be demonstrated in animal models, but only at doses considerably in excess of those required for analgesia. Acetaminophen is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery, perhaps because of the high concentrations of peroxides that are found in inflammatory lesions (Marshall *et al.*, 1987).

Subjective Effects and Liability for Abuse. Phenacetin has been said to cause relaxation, drowsiness, euphoria, stimulation, and increased efficiency; such effects have been thought to contribute to its liability for abuse. In patients, minor subjective effects may well occur secondary to relief of pain or fever. Restlessness and excitement may occur for 3 or 4 days after discontinuation of long-term administration of phenacetin.

Other Effects. Single or repeated therapeutic doses of phenacetin or acetaminophen have no effect on the cardiovascular and respiratory systems. Acid–base changes do not occur. Neither drug produces the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. They have no effects on platelets, bleeding time, or the excretion of uric acid.

Pharmacokinetics and Metabolism. Acetaminophen and phenacetin are metabolized primarily by the hepatic microsomal enzymes. The metabolic pathways for the two drugs are rather different, except, of course, that a considerable proportion of phenacetin is dealkylated to acetaminophen.

Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the half-life in plasma is about 2 hours after therapeutic doses. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20 to 50% may be bound at the concentrations encountered during acute intoxication. After therapeutic doses, 90 to 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites have also been detected. Children have less capacity for glucuronidation of the drug than do adults. A small proportion of acetaminophen undergoes cytochrome P_{450}-mediated N-hydroxylation to form N-acetyl-benzoquinoneimine, a highly reactive intermediate (*see* Figure 1–4, page 19). This metabolite normally reacts with sulfhydryl groups in glutathione. However, after large doses of acetaminophen the metabolite is formed in amounts sufficient to deplete hepatic glutathione; under these circumstances, reaction with sulfhydryl groups in hepatic proteins is increased and hepatic necrosis can result.

In the normal individual, 75 to 80% of phenacetin is rapidly metabolized to acetaminophen (*see* Table 26–2). The peak concentration of phenacetin in plasma usually occurs in about 1 hour and that of acetaminophen derived therefrom in 1 to 2 hours. Phenacetin is converted to at least a dozen other metabolites, by N-deacetylation to para-phenetidin and by hydroxylation and further metabolism of phenacetin and para-phenetidin. An unknown metabolite, but an oxidizing agent, is responsible for formation of methemoglobin and hemolysis of red

blood cells. Individuals with a genetically determined limitation in their ability to metabolize phenacetin to acetaminophen convert a greater fraction of phenacetin to toxic metabolites, possibly with propensity for serious methemoglobin formation and hemolysis. Less than 1% of phenacetin is excreted unchanged in the urine.

Toxic Effects. In recommended therapeutic dosage, acetaminophen and phenacetin are usually well tolerated. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions. Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to acetaminophen and related drugs (Szczeklik, 1986; Stevenson and Lewis, 1987). In a few isolated cases, the use of acetaminophen has been associated with neutropenia, thrombocytopenia, and pancytopenia.

Despite the fact that acetaminophen is a metabolite of phenacetin, the signs and symptoms of acute intoxication with the two compounds are markedly different. The most serious adverse effect of acute overdosage of acetaminophen is a dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis (also seen with phenacetin) and hypoglycemic coma may also occur. Phenacetin may cause methemoglobinemia and hemolytic anemia as a form of acute toxicity, but more commonly as a consequence of chronic overdosage. Lethal doses of phenacetin are not associated with hepatic damage, but with cyanosis, respiratory depression, and cardiac arrest. Acetaminophen is much less likely to cause the formation of methemoglobin and has not been incriminated in the hemolytic reactions. The nephrotoxicity associated with chronic abuse of acetaminophen, phenacetin, and other analgesics has been discussed above.

Hepatotoxicity. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (150 to 250 mg/kg) of acetaminophen; doses of 20 to 25 g or more are potentially fatal. The mechanism of this effect is discussed above (*see also* Chapter 1). Symptoms during the first 2 days of acute poisoning by acetaminophen may not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia, and abdominal pain occur during the initial 24 hours and may persist for a week or more. Clinical indications of hepatic damage become manifest within 2 to 4 days of ingestion of toxic doses. Initially, plasma transaminases are elevated (sometimes markedly so), and the concentration of bilirubin in plasma may be increased; in addition, the prothrombin time is prolonged. Perhaps 10% of poisoned patients who do not receive specific treatment develop severe liver damage; of these, 10 to 20% eventually die of hepatic failure. Acute renal failure also occurs in some patients. Biopsy of the liver reveals centrilobular necrosis with sparing of the periportal area. In nonfatal cases, the hepatic lesions are reversible over a period of weeks or months.

Severe liver damage (with levels of aspartate aminotransferase activity in excess of 1000 I.U. per liter of plasma) occurs in 90% of patients with plasma concentrations of acetaminophen greater than 300 μg/ml at 4 hours or 45 μg/ml at 15 hours after the ingestion of the drug. Minimal hepatic damage can be anticipated when the drug concentration is less than 120 μg/ml at 4 hours or 30 μg/ml at 12 hours after ingestion. The potential severity of hepatic necrosis can also be predicted from the half-life of acetaminophen observed in the patient; values greater than 4 hours imply that necrosis will occur, while values greater than 12 hours suggest that hepatic coma is likely.

Treatment. Early diagnosis is vital in the treatment of overdosage with acetaminophen, and methods are available for the rapid determination of concentrations of the drug in plasma. However, therapy should not be delayed while awaiting laboratory results if the history suggests a significant overdosage. Vigorous supportive therapy is essential when intoxication is severe. Gastric lavage should be performed in all cases, preferably within 4 hours of the ingestion. Activated charcoal is usually *not* administered because it can absorb the antidote, N-acetylcysteine, and reduce its efficacy (*see* below).

The principal antidotal treatment is the administration of sulfhydryl compounds, which probably act, in part, by replenishing hepatic stores of glutathione. N-acetylcysteine is particularly effective when given orally. The drug is recommended if less than 24 hours has elapsed since ingestion of acetaminophen, although treatment with N-acetylcysteine is more effective when given less than 10 hours after ingestion (Smilkstein *et al.*, 1988). An oral loading dose of 140 mg/kg is given, followed by the administration of 70 mg/kg every 4 hours for 17 doses. Treatment should begin immediately upon suspecting a significant acetaminophen overdosage, and it is terminated if assays of acetaminophen in plasma indicate that the risk of hepatotoxicity is low. *Acetylcysteine* (MUCOMYST, MUCOSOL) is available as a sterile 10 or 20% solution in vials containing 4, 10, and 30 ml. The solution is diluted with soft drinks or water to achieve a 5% solution and should be consumed within 1 hour of preparation. An intravenous form of acetylcysteine is available in Europe, where it is considered the treatment of choice. Consultation may be obtained from the Rocky Mountain Poison Center, Denver,

Colorado (Tel.: 800–525–6115). (*See* Prescott and Critchley, 1983; Smilkstein *et al.*, 1988.)

Other Toxic Effects. Phenacetin-induced hemolytic anemia and the methemoglobinemia that follows poisoning with acetanilide or phenacetin are discussed in *earlier editions* of this textbook.

Preparations, Routes of Administration, and Dosage. *Acetaminophen* (*paracetamol*; N-acetyl-*p*-aminophenol) is marketed under many trade names (*e.g.*, TEMPRA, TYLENOL). Preparations include tablets (160, 325, 500, 650 mg), capsules (325 and 500 mg), suppositories, chewable tablets, wafers, elixirs, and solutions. The conventional oral dose of acetaminophen is 325 to 1000 mg (650 mg rectally); the total daily dose should not exceed 4000 mg. For children, the single dose is 40 to 480 mg, depending upon age and weight; no more than five doses should be administered in 24 hours. A dose of 10 mg/kg may also be used. Acetaminophen should not be administered for more than 10 days or to young children except upon advice of a physician.

Phenacetin has been employed only in analgesic mixtures. In recent years it has been removed from almost all such mixtures. In some instances acetaminophen has been included to replace it.

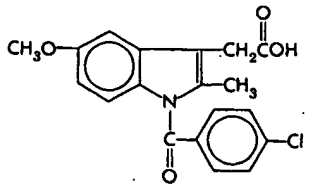
Therapeutic Uses. Acetaminophen is a suitable substitute for aspirin for its analgesic or antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicated (*e.g.*, those with peptic ulcer) or when the prolongation of bleeding time caused by aspirin would be a disadvantage.

INDOMETHACIN AND SULINDAC

Indomethacin was the product of a laboratory search for drugs with antiinflammatory properties. It was introduced in 1963 for the treatment of rheumatoid arthritis and related disorders. Although indomethacin is widely used and is effective, toxicity often limits its use. Sulindac was developed in an attempt to find a less toxic but effective congener of indomethacin. The development, chemistry, and pharmacology of both drugs have been reviewed by Rhymer and Gengos (Symposium, 1983a) and by Shen (Rainsford, 1985a).

INDOMETHACIN

Chemistry. The structural formula of indomethacin, a methylated indole derivative, is as follows:



Indomethacin

Pharmacological Properties. Indomethacin has prominent antiinflammatory and analgesic–antipyretic properties similar to those of the salicylates.

The antiinflammatory effects of indomethacin are evident in patients with rheumatoid and other types of arthritis, including acute gout. Although indomethacin is more potent than aspirin, doses that are tolerated by patients with rheumatoid arthritis usually do not produce effects that are superior to those of salicylate. Indomethacin has analgesic properties distinct from its antiinflammatory effects, and there is evidence for both a central and a peripheral action; it is also an antipyretic.

Indomethacin is a potent inhibitor of the prostaglandin-forming cyclooxygenase; it also inhibits the motility of polymorphonuclear leukocytes. Like many other aspirin-like drugs, indomethacin uncouples oxidative phosphorylation in supratherapeutic concentrations and depresses the biosynthesis of mucopolysaccharides.

Pharmacokinetics and Metabolism. Indomethacin is rapidly and almost completely absorbed from the gastrointestinal tract after oral ingestion. The peak concentration in plasma is attained within 2 hours in the fasting subject but may be somewhat delayed when the drug is taken after meals. The concentrations in plasma required for an antiinflammatory effect have not been definitely determined but are probably less than 1 μg/ml. Steady-state concentrations in plasma after long-term administration are approximately 0.5 μg/ml. Indomethacin is 90% bound to plasma proteins and also extensively bound to tissues. The concentration of the drug in the CSF is low, but its concentration in synovial fluid is equal to that in plasma within 5 hours of administration.

Indomethacin is largely converted to inactive metabolites, including those formed by O-demethylation (about 50%), conjugation with glucuronic acid (about 10%), and N-deacylation. Some of these metabolites are detectable in plasma, and free and conjugated metabolites are eliminated in the

urine, bile, and feces. There is enterohepatic cycling of the conjugates and probably of indomethacin itself. Ten to 20% of the drug is excreted unchanged in the urine, in part by tubular secretion. The half-life in plasma is variable, perhaps because of enterohepatic cycling, but averages about 3 hours.

Drug Interactions. The total plasma concentration of indomethacin plus its inactive metabolites is increased by concurrent administration of probenecid, possibly because of reduced tubular secretion of the former. However, it has not been determined whether the dosage of indomethacin must be adjusted when the two drugs are employed together. Indomethacin does not interfere with the uricosuric effect of probenecid. Indomethacin is said not to modify the effect of the oral anticoagulant agents. However, concurrent administration could be hazardous because of the increased risk of gastrointestinal bleeding. Indomethacin antagonizes the natriuretic and antihypertensive effects of furosemide; the antihypertensive effects of thiazide diuretics, β-adrenergic blocking agents, or inhibitors of angiotensin converting enzyme may also be reduced. Acute renal failure associated with the concomitant administration of indomethacin and triamterene has been reported (*see* Clive and Stoff, 1984).

Toxic Effects. A very high percentage (35 to 50%) of patients receiving usual therapeutic doses of indomethacin experience untoward symptoms, and about 20% must discontinue its use. Most adverse effects are dose related.

Gastrointestinal complaints and complications consist of anorexia, nausea, and abdominal pain. Single ulcers or multiple ulceration of the entire upper gastrointestinal tract, sometimes with perforations and hemorrhage, has been reported. Occult blood loss may lead to anemia in the absence of ulceration. Acute pancreatitis has also been reported. Diarrhea may occur and is sometimes associated with ulcerative lesions of the bowel. Hepatic involvement is rare, although some fatal cases of hepatitis and jaundice have been reported. The most frequent CNS effect (indeed, the most common side effect) is severe frontal headache, occurring in 25 to 50% of patients who take the drug for long periods. Dizziness, vertigo, light-headedness, and mental confusion are also frequent. Severe depression, psychosis, hallucinations, and suicide have occurred.

Hematopoietic reactions include neutropenia, thrombocytopenia, and, rarely, aplastic anemia. Platelet function is impaired by indomethacin. Hypersensitivity reactions are manifested as rashes, itching, urticaria, and, more seriously, acute attacks of asthma. Patients sensitive to aspirin may exhibit cross-reactivity to indomethacin. Indomethacin should not be used in pregnant women, nursing mothers, persons operating machinery, or patients with psychiatric disorders, epilepsy, or parkinsonism. It is also contraindicated in individuals with renal disease or ulcerative lesions of the stomach or intestines.

Preparations, Routes of Administration, and Dosage. *Indomethacin* (INDOCIN, others) is available for oral use in capsules containing 25, 50, or 75 mg of the drug, and in sustained-release capsules (75 mg); it is also supplied in 50-mg suppositories and as an oral suspension (25 mg/5 ml).

The initial dose is 25 mg, two or three times daily, and this can be increased in 25- or 50-mg increments at weekly intervals until the total daily dose is 150 to 200 mg. Few patients tolerate more than 150 mg per day without severe side effects. Most patients respond within 4 to 6 days, but some require substantially longer treatment. The drug should be taken in divided portions with food or antacids or immediately after meals to lessen gastric distress. A dose of indomethacin taken with milk at bedtime is said to reduce the incidence of morning headache.

Indomethacin is also available for intravenous injection as the sodium trihydrate (INDOCIN I.V.) to induce closure of a patent ductus arteriosus in neonates.

Therapeutic Uses. Because of the high incidence and severity of side effects associated with long-term administration, indomethacin must not be routinely used as an analgesic or antipyretic. However, it has proven useful as an antipyretic in certain settings (*e.g.*, Hodgkin's disease) when the fever has been refractory to other agents. Indomethacin has become an accepted part of the rheumatologist's armamentarium and a standard (together with aspirin) against which to measure the activity of other, newer drugs.

Clinical trials of indomethacin as an antiinflammatory agent have been reviewed by Rhymer and Gengos (in Symposium, 1983a). The majority of these trials have demonstrated that indomethacin relieves pain, reduces swelling and tenderness of the joints, increases grip strength, and decreases the duration of morning stiffness. In these actions the drug is superior to placebo and equivalent to phenylbutazone; estimates of its potency relative to salicylates vary between 10 and 40 times higher. Overall, about two thirds of patients benefit from treatment with indomethacin; however, if 75 to 100 mg of the drug fails to provide benefit within 2 to 4 weeks, alternative therapy must be considered. The incidence and severity of side effects with indomethacin are particularly annoying, but a useful way of employing the undoubted potency of the drug, perhaps in combination with other and better-tolerated daytime therapy, is to give a large single dose (up to 100 mg) at bedtime. This enables the patient to obtain a better-quality sleep, reduces the severity and length of morning stiffness, and pro-

vides good analgesia until midmorning. The side effects of indomethacin are apparently better tolerated when it is given at night.

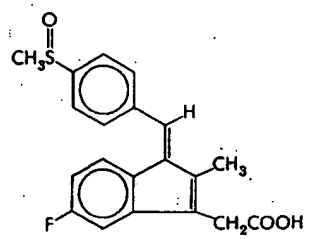
Indomethacin is often more effective than aspirin in the treatment of ankylosing spondylitis and osteoarthrosis. It is also very effective in the treatment of acute gout, although it is not uricosuric.

Patients with Bartter's syndrome have been successfully treated with indomethacin, as well as with other inhibitors of prostaglandin synthetase (*see* Clive and Stoff, 1984). The results are frequently dramatic; however, the condition of the patients may deteriorate rapidly when therapy is discontinued, and the long-term therapy necessary to control the disease requires administration of a drug that is better tolerated.

Cardiac failure in neonates caused by a patent ductus arteriosus may be controlled by the administration of indomethacin. A typical regimen involves the intravenous administration of 0.1 to 0.2 mg/kg every 12 hours for three doses. Successful closure can be expected in more than 70% of neonates who are treated with the drug. Such therapy is indicated primarily in premature infants who weigh between 500 and 1750 g, who have a hemodynamically significant patent ductus arteriosus, and in whom other supportive maneuvers have been attempted. The principal limitation of this approach is renal toxicity, and therapy is stopped if the output of urine falls below 0.6 ml/kg per hour. Renal failure, enterocolitis, thrombocytopenia, or hyperbilirubinemia contraindicates the use of indomethacin.

SULINDAC

Chemistry. Sulindac is closely related to indomethacin; its structural formula is as follows:



Sulindac

It is unlikely that sulindac itself has much therapeutic efficacy; most of its pharmacological activity resides in its sulfide metabolite.

Pharmacological Properties. In laboratory studies, sulindac exhibits the classical activities of aspirin-like drugs. In all tests, sulindac is less than half as potent as indomethacin.

Because sulindac is a prodrug, it appears to be either inactive or relatively weak in many tests, whereas its sulfide metabolite may be very active. This especially applies to tests where little or no metabolism can occur. The sulfide metabolite is more than 500 times more potent than sulindac as an inhibitor of cyclooxygenase. These observations may help to explain the somewhat lower incidence of gastrointestinal toxicity of sulindac as compared with indomethacin, since the gastric or intestinal mucosa is not exposed to high concentrations of an active drug during oral administration. Nevertheless, gastrointestinal toxicity is more common with sulindac than with many other aspirin-like drugs. Sulindac may also be unusual in that some clinical studies indicate that it does not alter the urinary excretion of prostaglandins or alter renal function (*see* Patrono and Dunn, 1987). However, if a "renal-sparing" effect exists, it is only relative, and the drug must be used with caution in patients who are dependent upon the synthesis of prostaglandins in the kidney for maintenance of renal function (*see* above).

Pharmacokinetics and Metabolism. The metabolism and pharmacokinetics of sulindac are complex and vary enormously among species. After oral administration in man, about 90% of the drug is absorbed. Peak concentrations of sulindac in plasma are attained within 1 hour, while those of the sulfide metabolite occur about 2 hours after the oral administration of sulindac.

Sulindac undergoes two major biotransformations in addition to conjugation reactions. It is oxidized to the sulfone and then reversibly reduced to the sulfide. It is this latter metabolite that is the active moiety, although all three compounds are found in comparable concentrations in human plasma. The half-life of sulindac itself is about 7 hours, but the active sulfide has a half-life as long as 18 hours. Sulindac and its metabolites undergo extensive enterohepatic circulation. There seems to be little or no placental transfer of the drug, but it is present in breast milk. Sulindac and the sulfone and sulfide metabolites are all extensively bound to plasma protein.

Little of the sulfide or its conjugates is found in urine. The principal components that are excreted in urine are the sulfone and its conjugate, which account for nearly 30% of an administered dose; sulindac and its conjugates account for about 20%. Up to 25% of an oral dose may appear as metabolites in the feces.

Preparations, Route of Administration, and Dosage. *Sulindac* (CLINORIL) is available as 150- and 200-mg tablets. The most common dosage for adults is 150 to 200 mg twice a day, although dosage should be optimized for each individual. The maximal daily dose is 400 mg. The drug is usually given with food to reduce gastric discomfort, although this may delay absorption and reduce the concentration in plasma.

Toxic Effects. Although the incidence of toxicity is lower than with indomethacin, untoward reactions to sulindac are common.

Gastrointestinal side effects are seen in nearly 20% of patients, although these are generally mild. Abdominal pain and nausea are the most frequent complaints. CNS side effects are seen in up to 10% of patients, with drowsiness, dizziness, headache, and nervousness being those most frequently reported. Skin rash and pruritus occur in 5% of patients. Transient elevations of hepatic enzymes in plasma are less common. Sulindac can precipitate a severe reaction in patients who are sensitive to aspirin; platelet function may also be impaired and bleeding time prolonged.

Therapeutic Uses. Sulindac has been used mainly for the treatment of rheumatoid arthritis, osteoarthrosis, and ankylosing spondylitis. The drug has also been used with success in the treatment of acute gout. The analgesic and antiinflammatory effects exerted by sulindac (400 mg per day) are comparable to those achieved with aspirin (4 g per day), ibuprofen (1200 mg per day), indomethacin (125 mg per day), and phenylbutazone (400 to 600 mg per day) (*see* Rhymer, in Symposium, 1983a).

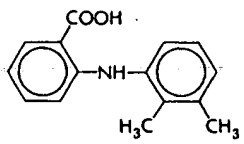
THE FENAMATES

The fenamates are a family of aspirin-like drugs that are derivatives of N-phenylanthranilic acid. They include mefenamic, meclofenamic, flufenamic, tolfenamic, and etofenamic acids.

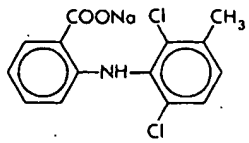
Although the biological activity of this group of drugs was discovered in the 1950s, the fenamates have not gained widespread clinical acceptance. They frequently cause side effects; diarrhea, in particular, may be very severe. Therapeutically, they also have no clear advantages over several other aspirin-like drugs.

Mefenamic acid and meclofenamate are the only members of the series available in the United States. The use of mefenamic acid is indicated only for analgesia and for relief of the symptoms of primary dysmenorrhea. While meclofenamate is employed in the treatment of rheumatoid arthritis and osteoarthritis, it is not recommended as initial therapy. Flufenamic acid is used in many other countries, as is mefenamic acid, for its antiinflammatory effects. Other members of the series will not be discussed further.

Chemistry. Mefenamic acid and meclofenamate are both N-substituted phenylanthranilic acids. Their structures are as follows:



Mefenamic Acid



Meclofenamate Sodium

Pharmacological Properties. In tests of antiinflammatory activity, mefenamic acid is about half as potent and flufenamic acid about 1.5 times as potent as phenylbutazone. Both drugs also have antipyretic and analgesic properties. In tests of analgesia, mefenamic acid was the only fenamate to display a central as well as a peripheral action.

The fenamates appear to owe these properties to their capacity to inhibit cyclooxygenase. Unlike the other aspirin-like drugs, certain of the fenamates (especially meclofenamic acid) also appear to antagonize certain effects of prostaglandins.

Pharmacokinetic Properties. Peak concentrations in plasma are reached in 0.5 to 2 hours after a single oral dose of meclofenamate and in 2 to 4 hours for mefenamic acid. The two agents have similar half-lives in plasma (2 to 4 hours). In man, approximately 50% of a dose of mefenamic acid is excreted in the urine, primarily as the conjugated 3-hydroxymethyl metabolite and the 3-carboxyl metabolite and its conjugates. Twenty percent of the drug is recovered in the feces, mainly as the unconjugated 3-carboxyl metabolite.

Preparations, Route of Administration, and Dosage. *Mefenamic acid* (PONSTEL) is available in 250-mg capsules for oral administration. For acute pain, the initial dose is 500 mg; thereafter, 250 mg may be given every 6 hours with food. The drug is not recommended for use in children or pregnant women, and it should not be given for longer than 7 days. *Meclofenamate sodium* (MECLOMEN) is available in capsules or tablets containing the equivalent of 50 or 100 mg of meclofenamic acid. The usual daily dose is 200 to 400 mg in three or four portions. Dosage requires adjustment for the individual but should not exceed 400 mg per day. The drug is not recommended for children.

Toxic Effects and Precautions. The most common side effects (occurring in approximately 25% of all patients) involve the gastrointestinal system. Usually these take the form of dyspepsia or upper gastrointestinal discomfort, although diarrhea, which may be severe and associated with steatorrhea and inflammation of the bowel, is also relatively common.

Other reactions that have been noted less frequently include transient abnormalities of hepatic and renal function, CNS effects, and skin rashes. A potentially serious side effect seen in isolated cases is a hemolytic anemia, which may be of an autoimmune type.

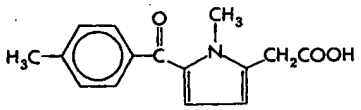
The fenamates are contraindicated in patients with a history of gastrointestinal disease. If diar-

rhea or skin rash appears, the drug should be stopped at once. The physician and patient should watch for signs of hemolytic anemia. The fenamates can cause bronchoconstriction in patients who are sensitive to aspirin and can affect platelet function.

Therapeutic Uses. As an analgesic agent, mefenamic acid has been used to relieve pain arising from rheumatic conditions, soft-tissue injuries, other painful musculoskeletal conditions, and dysmenorrhea. Toxicity limits its usefulness and it appears to offer no advantage over other analgesic agents. As antiinflammatory agents, mefenamic acid and meclofenamate have been mainly tested in short-term trials in the treatment of osteoarthritis and rheumatoid arthritis and appear to offer no advantage over other aspirin-like drugs.

TOLMETIN

Tolmetin is an antiinflammatory, analgesic, and antipyretic agent that was introduced into clinical practice in the United States in 1976. Tolmetin, in recommended doses, appears to be approximately equivalent in efficacy to moderate doses of aspirin; it is usually better tolerated. The structural formula of tolmetin is as follows:



Tolmetin

Pharmacological Properties. Tolmetin is an effective antiinflammatory agent that also exerts antipyretic and analgesic effects. Like most of the other drugs considered in this chapter, tolmetin causes gastric erosions and prolongs bleeding time. The pharmacology of tolmetin has been reviewed by Ehrlich (in Symposium, 1983a) and by Wong (Rainsford, 1985b).

Pharmacokinetics and Metabolism. Tolmetin is rapidly and completely absorbed after oral administration in man; the concentrations achieved in plasma are not reduced by the concomitant administration of antacids. Peak concentrations are achieved 20 to 60 minutes after oral administration, and the half-life in plasma is about 5 hours. Accumulation of the drug in synovial fluid begins within 2 hours and persists for up to 8 hours after a single oral dose.

After absorption, tolmetin is extensively (99%) bound to plasma proteins. Virtually all of the drug can be recovered in the urine after 24 hours; some is unchanged but most is conjugated or otherwise metabolized. The major metabolic transformation involves oxidation of the para-methyl group to a carboxylic acid.

Preparations, Route of Administration, and Dosage. *Tolmetin sodium* (TOLECTIN) is supplied as 200-mg tablets and 400-mg capsules for oral use. The recommended initial dose is 400 mg three times daily, and it is suggested that one of these doses be taken at bedtime and another on awakening. The response to the drug is usually seen within a week, and the dose can then be adjusted; the usual range is 600 to 1800 mg per day in divided doses. The maximal recommended dose is 2 g per day. The drug may be given with meals, milk, or antacids other than sodium bicarbonate to lessen abdominal discomfort; however, peak plasma concentrations and bioavailability are significantly reduced when taken with food. The recommended initial daily dose for children (2 years and older) is 20 mg/kg per day in three or four divided doses. Maintenance dosage ranges from 15 to 30 mg/kg per day.

Toxic Effects. Side effects occur in 25 to 40% of patients who take tolmetin, and 5 to 10% discontinue use of the drug. Gastrointestinal side effects are the most common, with epigastric pain (15% incidence), dyspepsia, nausea, and vomiting being the chief manifestations. Gastric and duodenal ulceration has also been observed. CNS side effects, including nervousness, anxiety, insomnia, drowsiness, and visual disturbance, are less common and are said to be neither as frequent nor as severe as those caused by indomethacin. Similarly, the incidence of tinnitus, deafness, and vertigo is less than occurs with aspirin. It should be assumed that tolmetin will probably precipitate bronchoconstriction in patients who are hypersensitive to aspirin. In addition, there have been several reports of severe anaphylactoid reactions to tolmetin in patients who are not sensitive to aspirin and other aspirin-like drugs.

Drug Interactions. Despite its extensive binding to albumin, tolmetin does not interfere with concurrent treatment with warfarin or oral hypoglycemic agents.

Therapeutic Uses. Tolmetin is approved in the United States for the treatment of osteoarthritis, rheumatoid arthritis, and the juvenile form of the disease; it has also been used in the treatment of ankylosing spondylitis. In rheumatoid arthritis, many investigators have compared tolmetin (0.8 to 1.6 g per day) with aspirin (4 to 4.5 g per day) or indomethacin (100 to 150 mg per day). In general, there has been little difference in therapeutic efficacy. Tolmetin may be tolerated somewhat better than aspirin in equally effective doses. Similar results have been obtained with related arthritides and with soft-tissue injuries (*see* Ehrlich, in Symposium, 1983a).

PROPIONIC ACID DERIVATIVES

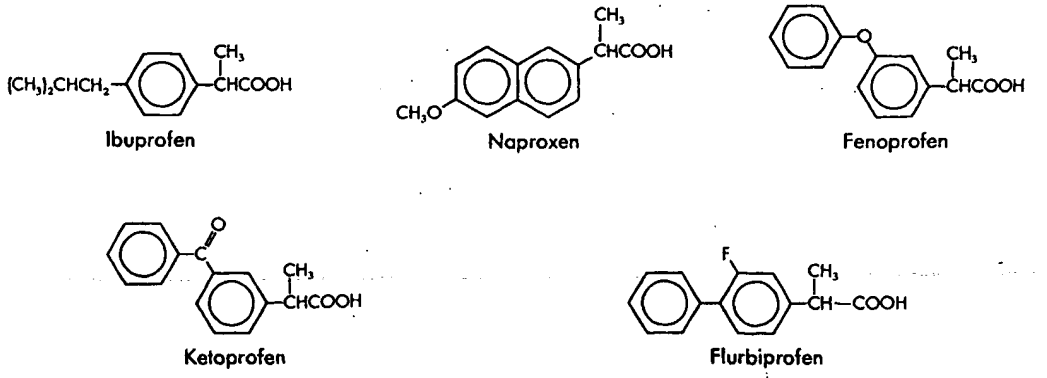
These drugs represent a group of effective, useful aspirin-like agents. They may offer significant advantages over aspirin, indomethacin, and the pyrazolon derivatives for many patients, since they are usually better tolerated. Nevertheless, propionic acid derivatives share all of the detrimental features of the entire class of drugs. Furthermore, their rapid proliferation in number and heavy promotion of these drugs make it difficult for the physician to choose rationally between members of the group and between propionic acid derivatives and the more established agents. The similarities between drugs in this class (and certain of the others discussed above) are far more striking than are the differences.

Ibuprofen, naproxen, flurbiprofen, fenoprofen, and ketoprofen are described individually below. These drugs are currently available in the United States, but several additional agents in this class are in use or under study in other countries. These include fenbufen, pirprofen, oxaprozin, indoprofen, and tiaprofenic acid. Ibuprofen was the first member of this class to come into general use, so experience with this drug is greater. It is available for sale without a prescription in the United States. The most distinctive feature among the others may probably be claimed by naproxen; its longer half-life makes twice-daily administration feasible. The structural formulas of these drugs are shown in Table 26–3.

Pharmacological Properties. The pharmacodynamic properties of the propionic acid derivatives do not differ significantly. While the compounds do vary in potency, this is not of obvious clinical significance. All are effective antiinflammatory agents in various experimental models of inflammation in animals; all have useful antiinflammatory, analgesic, and antipyretic activity in man.

All of these compounds can cause gastrointestinal erosions (gastric, duodenal, and intestinal) in experimental animals. All pro-

Table 26–3. STRUCTURAL FORMULAS OF ANTIINFLAMMATORY PROPIONIC ACID DERIVATIVES



duce gastrointestinal side effects in man, although these are usually less severe than with aspirin. Certain propionic acid derivatives (*e.g.*, penoxaprofen) have produced a high incidence of hepatotoxicity, which has led to their removal from the market. The possibility that this may occur with other drugs in this class must be considered.

The propionic acid derivatives are effective inhibitors of the cyclooxygenase responsible for the biosynthesis of prostaglandins, although there is considerable variation in their potency. For example, naproxen is approximately 20 times more potent than aspirin, while ibuprofen, fenoprofen, and aspirin are roughly equipotent in this action. All of these agents alter platelet function and prolong bleeding time, and it should be assumed that any patient who is intolerant of aspirin may also suffer a severe reaction after administration of one of these drugs. Some of the propionic acid derivatives have prominent inhibitory effects on the migration and other functions of leukocytes. Naproxen is particularly potent in this regard.

Drug Interactions. The potential adverse drug interactions of particular concern with this group derive from their high degree of binding to albumin in plasma. However, the propionic acid derivatives do not alter the effects of the oral hypoglycemic drugs or warfarin. Nevertheless, the physician should be prepared to adjust the dosage of warfarin because these drugs impair platelet function and may cause gastrointestinal lesions.

As discussed above, the propionic acid derivatives can be expected to reduce the diuretic and natriuretic effects of furosemide as well as the antihypertensive effects of such agents as the thiazide diuretics, β-adrenergic antagonists, and inhibitors of angiotensin converting enzyme (*see* Clive and Stoff, 1984; Oates *et al.*, 1988). These effects probably result from the inhibition of the synthesis of renal or vascular prostaglandins (*see* above).

IBUPROFEN

Ibuprofen has been discussed in detail by Kantor (1979) and by Adams and Buckler (in Symposium, 1983a).

Pharmacokinetics and Metabolism. Ibuprofen is rapidly absorbed after oral administration in man, and peak concentrations in plasma are observed after 1 to 2 hours. The half-life in plasma is about 2 hours. Absorption is also efficient, although slower, from suppositories.

Ibuprofen is extensively (99%) bound to plasma proteins, but the drug occupies only a fraction of the total drug-binding sites at usual concentrations. Ibuprofen passes slowly into the synovial spaces and may remain there in higher concentration as the concentrations in plasma decline. In experimental animals, ibuprofen and its metabolites pass easily across the placenta.

The excretion of ibuprofen is rapid and complete. More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, and no ibuprofen *per se* is found in the urine. The major metabolites are a hydroxylated and a carboxylated compound.

Preparations, Route of Administration, and Dosage. *Ibuprofen* (MOTRIN, RUFEN) is supplied as tablets containing 200 to 800 mg; only the 200-mg tablets (ADVIL, NUPRIN, others) are available without a prescription.

For rheumatoid arthritis and osteoarthritis, daily doses of up to 3200 mg in divided portions may be given, although the usual total dose is 1200 to 1800 mg. It may also be possible to reduce the dosage for maintenance purposes. For mild-to-moderate pain, especially that of primary dysmenorrhea, the usual dosage is 400 mg every 4 to 6 hours as needed. The drug may be given with milk or food to minimize gastrointestinal side effects. The safety and efficacy of ibuprofen in children have not been established.

Toxic Effects. Ibuprofen has been used in patients with known peptic ulceration or a history of gastric intolerance to other aspirin-like agents. Nevertheless, therapy must usually be discontinued in 10 to 15% of patients because of intolerance to the drug.

Gastrointestinal side effects are experienced by 5 to 15% of patients taking ibuprofen; epigastric pain, nausea, heartburn, and sensations of "fullness" in the gastrointestinal tract are the usual difficulties. However, the incidence of these side effects is less with ibuprofen than with aspirin or indomethacin. Occult blood loss is uncommon.

Other side effects of ibuprofen have been reported less frequently. They include thrombocytopenia, skin rashes, headache, dizziness and blurred vision, and, in a few cases, toxic amblyopia, fluid retention, and edema. Patients who develop ocular disturbances should discontinue the use of ibuprofen.

Ibuprofen is not recommended for use by pregnant women, or by those who are breast-feeding their infants.

NAPROXEN

The pharmacological properties and therapeutic uses of naproxen have been reviewed by Segre (in Symposium, 1983a) and by Allison and colleagues (Rainsford, 1985b).

Pharmacokinetics and Metabolism. Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and may be achieved more rapidly after the administration of naproxen sodium. Absorption may be accelerated by the concurrent administration of sodium bicarbonate or reduced by magnesium oxide or aluminum hydroxide. Naproxen is also absorbed rectally, but peak concentrations in plasma are achieved more slowly. The half-life of naproxen in plasma is about 14 hours; this value is increased about twofold in elderly subjects and may necessitate adjustment of dosage.

Metabolites of naproxen are almost entirely excreted in the urine. About 30% of the drug undergoes 6-demethylation, and most of this metabolite, as well as naproxen itself, is excreted as the glucuronide or other conjugates.

Naproxen is almost completely (99%) bound to plasma protein following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration.

Preparations, Route of Administration, and Dosage. *Naproxen* (NAPROSYN) is available in 250-, 375-, and 500-mg tablets and a suspension (125 mg/5 ml) for oral administration. *Naproxen sodium* (ANAPROX) is marketed in tablets containing 275 or 550 mg of the salt (equivalent to 250 or 500 mg of naproxen). For rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, the usual dosage of naproxen is 250 to 500 mg, given twice daily; this is adjusted depending on the clinical response. For juvenile arthritis in children over 2 years of age, approximately 10 mg/kg per day is given in two divided doses. For acute gout, the usual initial dose of naproxen is 750 mg, followed by 250 mg every 8 hours until the attack has subsided. For mild-to-moderate pain, especially that associated with primary dysmenorrhea, bursitis, and acute tendinitis, the initial dose is 500 mg, followed by 250 mg every 6 to 8 hours. The drug may be given with meals if gastric discomfort is experienced.

Toxic Effects. Although the incidence of gastrointestinal and CNS side effects is about equal to that caused by indomethacin, naproxen is better tolerated in both regards. Gastrointestinal complications have ranged from relatively mild dyspepsia, gastric discomfort, and heartburn to nausea, vomiting, and gastric bleeding. CNS side effects range from drowsiness, headache, dizziness, and sweating to fatigue, depression, and ototoxicity. Less common reactions include pruritus and a variety of dermatological problems. A few instances of jaundice, impairment of renal function, angioneurotic edema, thrombocytopenia, and agranulocytosis have been reported.

FENOPROFEN

The pharmacological properties and therapeutic uses of fenoprofen have been reviewed by Burt and coworkers (Symposium, 1983a).

Pharmacokinetics and Metabolism. Oral doses of fenoprofen are readily, if incompletely (85%), absorbed. The presence of food in the stomach retards absorption and lowers peak concentrations in plasma, which are usually achieved within 2 hours. The concomitant administration of antacids does not seem to alter the concentrations that are achieved.

After absorption, fenoprofen is almost completely (99%) bound to plasma albumin. The drug is extensively (>90%) metabolized and excreted almost entirely in the urine. Fenoprofen undergoes metabolic transformation to the 4-hydroxy analog. The glucuronic acid conjugate of fenoprofen itself and 4-hydroxy fenoprofen are formed in almost equal amounts and together account for 90% of the excreted drug. The half-life of fenoprofen in plasma is about 3 hours.

Preparations, Route of Administration, and Dosage. *Fenoprofen calcium* (NALFON) is available in capsules and tablets containing 200 to 600 mg of the active drug for oral administration. The recommended dosage to treat rheumatoid ar-

thritis or osteoarthritis is 300 to 600 mg, given three to four times a day, but this may be increased to a maximum of 3.2 g per day. For mild-to-moderate pain, the usual dosage is 200 mg every 4 to 6 hours. Fenoprofen may be administered with meals. The drug is not currently recommended for children.

Toxic Effects. The most frequently reported side effects have been gastrointestinal ones; abdominal discomfort and dyspepsia occur in about 15% of patients. Constipation and nausea have also been reported. These side effects are almost always less intense than with equipotent doses of aspirin and force discontinuation of therapy in a small percentage of patients. Nevertheless, care should be exercised when giving the drug to patients with a history of gastrointestinal ulceration or other pathology. Other side effects include skin rash and, less frequently, CNS effects such as tinnitus, dizziness, lassitude, confusion, and anorexia.

KETOPROFEN

Ketoprofen shares the pharmacological properties of other propionic acid derivatives; these have been reviewed by Harris and Vávra (Rainsford, 1985b) and Vávra (Lewis and Furst, 1987). Although it is a cyclooxygenase inhibitor, ketoprofen is said to stabilize lysosomal membranes and it may antagonize the actions of bradykinin.

Pharmacokinetics and Metabolism. Ketoprofen is rapidly absorbed after oral administration and maximal concentrations in plasma are achieved within 1 to 2 hours; food reduces the rate but not the extent of absorption. The drug is extensively bound to plasma proteins (99%), and it has a half-life in plasma of about 2 hours; slightly longer half-lives are observed in elderly subjects. Ketoprofen is conjugated with glucuronic acid in the liver, and the conjugate is excreted in the urine. Patients with impaired renal function eliminate the drug more slowly.

Preparations, Route of Administration, and Dosage. *Ketoprofen* (ORUDIS) is available as 25-, 50-, and 75-mg capsules. The recommended daily dosage to treat arthritic conditions is 150 to 300 mg, given in three or four divided doses; the lowest effective dose should be used. For nonarthritic pain, 25 to 50 mg given every 6 to 8 hours may be sufficient.

Toxic Effects. Dyspepsia and other gastrointestinal side effects have been observed in about 30% of patients, but these side effects are generally mild and are less frequent than those in patients treated with aspirin; untoward effects are reduced when the drug is taken with food, milk, or antacids. Ketoprofen can cause fluid retention and increased plasma concentrations of creatinine. These effects are generally transient and occur in the absence of symptoms, but they are more common in patients who are receiving diuretics or in those over the age of 60. Renal function should be monitored in such patients.

FLURBIPROFEN

Flurbiprofen has been available for over a decade in various combination preparations, and the drug has recently been marketed as a single entity in the United States.

The pharmacological properties, therapeutic indications, and adverse effects of flurbiprofen are similar to those of other antiinflammatory derivatives of propionic acid (*see* Smith *et al.*, in Rainsford, 1985b). The drug is well absorbed orally, and peak plasma concentrations occur within 1 to 2 hours. Flurbiprofen is extensively metabolized by hydroxylation and conjugation in the liver; its half-life in plasma is about 6 hours.

Flurbiprofen (ANSAID) is available in 50- and 100-mg tablets. The recommended daily dosage for rheumatoid arthritis and osteoarthritis is 200 to 300 mg in two to four divided doses.

THERAPEUTIC USES

The approved indications for the use of one or another of the propionic acid derivatives include the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis; they are also used as analgesics, for acute tendinitis and bursitis, and for primary dysmenorrhea.

Clinical studies indicate that the propionic acid derivatives are comparable to aspirin for the control of the signs and symptoms of rheumatoid arthritis and osteoarthritis. In patients with rheumatoid arthritis there is a reduction in joint swelling, pain, and duration of morning stiffness. By objective measurements, strength, mobility, and stamina are improved. In general, the intensity of untoward effects is less than that associated with the ingestion of indomethacin or high doses of aspirin. However, aspirin is considerably less expensive for those who can tolerate it.

Although all of these agents may be of benefit in the treatment of ankylosing spondylitis, only naproxen has received approval for this use in the United States. As mentioned previously, naproxen appears to exert a prominent inhibitory effect on the migration of leukocytes; this may contribute to its efficacy in the treatment of acute attacks of gout. Clinical studies have indicated that the propionic acid derivatives may be as effective as aspirin in the treatment of juvenile arthritis. However, except for naproxen, the data are as yet insufficient to establish their safety for long-term use in children.

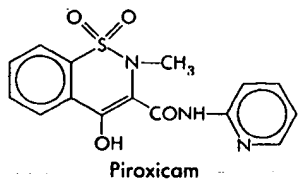
These agents are also effective for symptomatic relief from pain associated with injuries to soft tissues, and they have been used to relieve pain post partum and after oral, ophthalmic, and other types of surgery. Both ibuprofen and naproxen are more effective than aspirin for relief of pain from dysmenorrhea. Indeed, the effectiveness of ibuprofen

in this condition was one important reason for its release in 1984 for over-the-counter use.

It is difficult to find data on which to base a rational choice between the members of this group of drugs, if in fact one can be made. However, in studies that compared the activity of several members of this group, patients preferred naproxen in terms of analgesia and relief of morning stiffness (*see* Huskisson, in Symposium, 1983a; Hart and Huskisson, 1984). With regard to side effects, naproxen was the best tolerated, followed by ibuprofen and fenoprofen. There was considerable interpatient variation in the preference for a single drug and also between the designation of the best and the worst drug. Unfortunately, it is probably impossible to predict *a priori* which drug will be most suitable for any given individual. Nevertheless, more than 50% of patients with rheumatoid arthritis will probably achieve adequate symptomatic relief by the use of one or another of the propionic acid derivatives, and many clinicians favor their use instead of aspirin in such patients.

PIROXICAM

Piroxicam is one of the oxicam derivatives, a class of enolic acids that possesses antiinflammatory, analgesic, and antipyretic activity. Other oxicams have been developed and are under study (*e.g.*, tenoxicam). Piroxicam is the only drug in this class that is currently available in the United States. In recommended doses, piroxicam appears to be the equivalent of aspirin, indomethacin, or naproxen for the long-term treatment of rheumatoid arthritis or osteoarthritis. It may be tolerated better than aspirin or indomethacin. The principal advantage of piroxicam is its long half-life, which permits the administration of a single daily dose. The pharmacological properties and therapeutic uses of piroxicam have been reviewed in a symposium (Symposium, 1982), by Wiseman (Rainsford, 1985b), and by Lombardino and Wiseman (in Lewis and Furst, 1987). The structural formula of piroxicam is as follows:



Piroxicam

Pharmacological Properties. Piroxicam is an effective antiinflammatory agent; it is about equal in potency to indomethacin as an inhibitor of prostaglandin biosynthesis *in vitro*. Piroxicam can also inhibit activation of neutrophils even when products of cyclooxygenase are present; hence, additional modes of antiinflammatory action have been proposed (Abramson *et al.*, 1985; Lombardino and Wiseman, in Lewis and Furst, 1987). Piroxicam exerts antipyretic and analgesic effects in experimental animals and man. As with other aspirin-like drugs, piroxicam can cause gastric erosions and it prolongs bleeding time.

Pharmacokinetics and Metabolism. Piroxicam is completely absorbed after oral administration; peak concentrations in plasma occur within 2 to 4 hours. Neither food nor antacids alter the rate or extent of absorption. There is enterohepatic cycling of piroxicam, and estimates of the half-life in plasma have been variable; a mean value appears to be about 50 hours.

After absorption, piroxicam is extensively (99%) bound to plasma proteins. At steady state (*e.g.*, after 7 to 12 days), concentrations of piroxicam in plasma and synovial fluid are approximately equal. Less than 5% of the drug is excreted in the urine unchanged. The major metabolic transformation in man is hydroxylation of the pyridyl ring, and this inactive metabolite and its glucuronide conjugate account for about 60% of the drug excreted in the urine and feces.

Preparations, Route of Administration, and Dosage. *Piroxicam* (FELDENE) is available in 10- and 20-mg capsules for oral administration. The usual daily dose for the relief of signs and symptoms of rheumatoid arthritis or osteoarthritis is 20 mg; if desired, this may be given in two portions. Since steady-state concentrations in plasma are not reached for 7 to 12 days, maximal therapeutic responses should not be expected for 2 weeks, even though they may be evident earlier. It has been suggested that satisfactory responses are associated with concentrations in plasma of greater than 5 to 6 μg/ml.

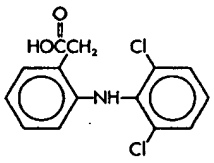
Toxic Effects. The reported incidence of adverse effects in patients who take piroxicam is about 20%; approximately 5% of patients stop using the drug because of side effects. Gastrointestinal reactions are the most common; the incidence of peptic ulcer is less than 1%. As with other aspirin-like

drugs, piroxicam alters the function of platelets, and it should be assumed that piroxicam will precipitate bronchoconstriction in patients who are hypersensitive to aspirin.

Therapeutic Uses. Piroxicam is approved in the United States for the treatment of rheumatoid arthritis and osteoarthritis. It has also been used in the treatment of ankylosing spondylitis, acute musculoskeletal disorders, dysmenorrhea, postoperative pain, and acute gout.

DICLOFENAC

Diclofenac is the first of a series of phenylacetic acid derivatives that have been developed as antiinflammatory agents. Details of its pharmacology are discussed in a symposium (Symposium, 1986b) and a review by Liauw and associates (in Lewis and Furst, 1987). The structure of diclofenac is as follows:



Diclofenac

Pharmacological Properties. Diclofenac possesses analgesic, antipyretic, and antiinflammatory activities; it is an inhibitor of cyclooxygenase, and its potency is substantially greater than that of indomethacin, naproxen, or several other agents. In addition, diclofenac appears to reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or uptake of the fatty acid.

Pharmacokinetics and Metabolism. Diclofenac is rapidly and completely absorbed after oral administration; peak concentrations in plasma are reached within 2 to 3 hours. Administration with food slows the rate but does not alter the extent of absorption. There is a substantial first-pass effect, such that only about 50% of diclofenac is available systemically. The drug is extensively bound to plasma proteins (99%), and its half-life in plasma is 1 to 2 hours. Diclofenac accumulates in synovial fluid after oral administration, which may explain the duration of therapeutic effect that is considerably longer than the plasma half-life. Diclofenac is metabolized in the liver to 4-hydroxydiclofenac, the principal metabolite, and other hydroxylated forms; after glucuronidation and sulfation, the metabolites are excreted in the urine (65%) and bile (35%).

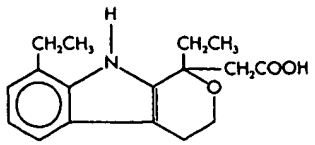
Preparations, Route of Administration, and Dosage. *Diclofenac sodium* (VOLTAREN) is available as 25-, 50-, and 75-mg enteric-coated tablets. For the symptomatic relief of rheumatoid arthritis, the usual daily dosage is 150 to 200 mg given in two to four divided portions; for osteoarthritis, 100 to 150 mg is given daily in two or three divided doses; for ankylosing spondylitis, 100 to 125 mg is given daily in four or five divided doses.

Toxic Effects. Diclofenac produces side effects in about 20% of patients, and approximately 2% of patients discontinue therapy as a result. Gastrointestinal effects are the most common, and bleeding and ulceration or perforation of the intestinal wall have been observed. Elevation of hepatic transaminase activities in plasma occurs in about 15% of patients. Although usually moderate, these values may increase more than threefold in a small percentage of patients—often those who are being treated for osteoarthritis. The elevations in transaminases are usually reversible and are only rarely associated with clinical evidence of hepatic disease. Transaminase activities should be evaluated during the first 8 weeks of therapy, and the drug should be discontinued if abnormal values persist or if other signs or symptoms develop. Other untoward responses to diclofenac include CNS effects, skin rashes, allergic reactions, fluid retention and edema, and rarely, impairment of renal function. The drug is not recommended for children, nursing mothers, or pregnant women.

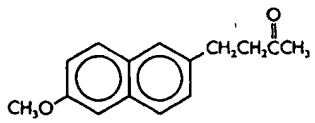
Therapeutic Uses. Diclofenac is approved in the United States for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It may also be useful for short-term treatment of acute musculoskeletal injury, acute painful shoulder (bicipital tendinitis and subdeltoid bursitis), postoperative pain, and dysmenorrhea.

OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUGS

A large number of antiinflammatory agents are under development or are under clinical study in the United States and elsewhere (*see* Rainsford, 1985b; Lewis and Furst, 1987). Although some are members of classes of drugs discussed above, others have novel structures and apparently different mechanisms of action. Two of the most important of these agents are etodolac and nabumetone; their structures are as follows:



Etodolac



Nabumetone

Etodolac. This compound is an inhibitor of cyclooxygenase, and it possesses antiinflammatory activity. However, there is an unusually large difference between doses that produce antiinflammatory effects and those that cause gastric irritation in experimental animals. This may result from a relatively limited effect on the production of PGE_2 in the gastric mucosa.

Etodolac is rapidly and well absorbed orally, and it is about 99% bound to plasma proteins. It is actively metabolized by the liver to various metabolites that are largely excreted in the urine. The drug may undergo enterohepatic circulation in man; its half-life in plasma is about 7 hours.

A single oral dose of etodolac provides postoperative analgesia that typically lasts for 6 to 8 hours. Etodolac also appears to be effective in the treatment of osteoarthritis and rheumatoid arthritis. Although gastrointestinal irritation and ulceration are the most common manifestations of toxicity, these side effects appear to occur less frequently with etodolac than with certain other aspirin-like drugs. About 5% of patients who have taken the drug for up to 1 year discontinue treatment because of side effects, which also include skin rashes and CNS effects. (For further discussion of etodolac, *see* Lynch and Brogden, 1986, and Lewis and Furst, 1987.)

Nabumetone. Nabumetone is a weak inhibitor of cyclooxygenase *in vitro*, but it is an active antiinflammatory drug in various experimental models; it also possesses antipyretic and analgesic activities. In experimental animals, nabumetone appears to cause less gastric damage than do other antiinflammatory agents.

Nabumetone is absorbed rapidly and is converted in the liver to one or more active metabolites, principally 6-methoxy-2-naphthylacetic acid, a potent inhibitor of cyclooxygenase. This metabolite is inactivated by O-demethylation in the liver and is then conjugated before excretion.

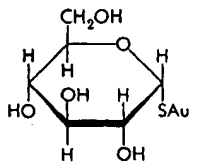
Clinical trials with nabumetone have indicated substantial efficacy in the treatment of rheumatoid arthritis and osteoarthritis, with a relatively low incidence of side effects. However, only small numbers of patients have received the drug for more than 1 year. The drug also appears to be effective in the short-term treatment of soft-tissue injuries.

Side effects of treatment with nabumetone include lower bowel complaints, skin rash, headache, dizziness, heartburn, tinnitus, and pruritus. Thus far, the incidence of gastric ulceration has been much lower with nabumetone than with other aspirin-like drugs. This may result from the fact that an active compound is generated only after absorption of the administered drug. (For further discussion of nabumetone, *see* Symposium, 1987b, and Friedel and Todd, 1988.)

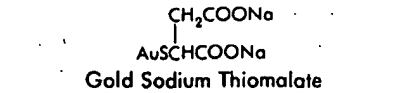
GOLD

Gold, in elemental form, has been employed for centuries as an antipruritic to relieve the itching palm. In more modern times, the observation by Robert Koch in 1890 that gold inhibited *Mycobacterium tuberculosis in vitro* led to trials in arthritis and lupus erythematosus, thought by some to be tuberculous manifestations. The favorable observations of Forestier (1929) were largely responsible for stimulating interest in gold therapy (chrysotherapy). At present, gold is employed in the treatment of rheumatoid arthritis; its use is usually reserved for patients with progressive disease who do not obtain satisfactory relief from therapy with aspirin-like drugs. However, gold compounds are among a small number of agents that are capable of arresting the progress of the disease and inducing apparent remissions in some patients; these are sometimes called disease-modifying drugs. Since degenerative lesions do not regress once formed, there is an increasing tendency to attempt to induce remission early in the course of the disease. Such therapy is most often initiated with gold.

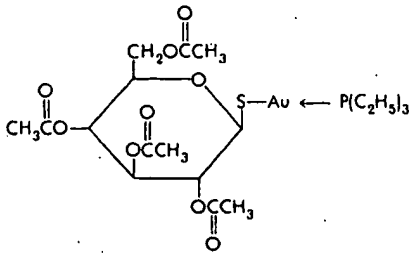
Chemistry. The significant preparations of gold are all compounds in which the gold is attached to sulfur. The more water-soluble compounds employed in therapy contain hydrophilic groups in addition to the aurothio group. The structural formulas of aurothioglucose, gold sodium thiomalate, and auranofin are as follows:



Aurothioglucose



Gold Sodium Thiomalate



Auranofin

Monovalent gold has a relatively strong affinity for sulfur, weak affinities for carbon and nitrogen, and almost no affinity for oxygen, except in chelates. The high affinity for sulfur and the inhibitory effect of gold salts on various enzymes have suggested that the therapeutic effects of gold salts might derive from inhibition of sulfhydryl systems. However, other sulfhydryl inhibitors do not appear to have therapeutic actions in common with gold.

Pharmacological Properties. Gold compounds can suppress or prevent, but not cure, experimental arthritis and synovitis due to a number of infectious and chemical agents. Gold compounds have minimal antiinflammatory effects in other circumstances and cause only a gradual reduction of the signs and symptoms of inflammation associated with rheumatoid arthritis. Although many effects of these drugs have been observed, which, if any, are related to the therapeutic effects of gold in rheumatoid arthritis is unknown. Perhaps the best hypotheses relate to the capacity of gold compounds to inhibit the maturation and function of mononuclear phagocytes, thereby suppressing immune responsiveness (*see* Tsokos, 1987). Decreased concentrations of rheumatoid factor and immunoglobulins are often observed in patients who are treated with gold.

In experimental animals, gold is sequestered in organs that are rich in mononuclear phagocytes, and it selectively accumulates in the lysosomes of type-A synovial cells and other macrophages within the inflamed synovium of patients who are treated with gold compounds. Moreover, the administration of gold thiomalate to animals depresses the migration and phagocytic activity of macrophages in inflammatory exudates, and chrysotherapy reduces the augmented phagocytic capacity of blood monocytes from patients with rheumatoid arthritis. Other mechanisms of action of gold compounds have been suggested, but none is generally accepted. These include inhibition of prostaglandin synthesis, interference with complement activation, cross-linking of collagen, and inhibition of the activity of lysosomal and other enzymes.

Absorption, Distribution, and Excretion. *Aurothioglucose and Gold Sodium Thiomalate.* These more water-soluble gold compounds are rapidly absorbed after intramuscular injection, and peak concentrations in blood are reached in 2 to 6 hours, unless the drug is suspended in oil. These agents are erratically absorbed when administered orally. Tissue distribution depends not only on the type of compound administered but also on the time after administration and probably on the duration of treatment. Early in the course of therapy, several percent of the total body content of gold is in the blood, where it is first bound (about 95%) to albumin, and the concentration in synovial fluid eventually reaches about half that in plasma. With continued therapy, the concentration of gold in the synovium of affected joints is about ten times that of skeletal muscle, bone, or fat. Gold deposits are also found in macrophages of many tissues, as well as in proximal tubular epithelium, seminiferous tubules, hepatocytes, and adrenocortical cells.

The pharmacokinetic properties of gold in these compounds are complex and vary with the dose and the duration of treatment. The plasma half-life is about 7 days for a 50-mg dose. With successive doses the half-life lengthens, and values of weeks or months may be observed after prolonged therapy, reflecting the avid binding of gold in tissues. After a cumulative dose of 1 g of gold, about 60% of the amount administered is retained in the body. After termination of treatment, urinary excretion of gold can be detected for as long as a year, even though concentrations in blood fall to the normal trace amounts in about 40 to 80 days. Substantial quantities of gold have been found in the liver and skin of patients many years after the cessation of therapy. The excretion of gold is 60 to 90% renal and 10 to 40% fecal, the latter probably mostly by biliary secretion. Sulfhydryl agents, such as dimercaprol, penicillamine, and N-acetylcysteine, increase the excretion of gold. The pharmacokinetics of gold has been reviewed by Blocka and coworkers (1986).

Auranofin. Auranofin is a more hydrophobic gold-containing compound that is more readily absorbed after oral administration (to the extent of about 25%). Steady-state concentrations of gold in plasma are proportional to the doses and are reached after 8 to 12 weeks of treatment. Therapeutic doses of auranofin (6 mg per day) lead to concentrations of gold in plasma that are generally lower than those achieved with conventional parenteral therapy, and the accumulation of gold during a 6-month course of treatment with auranofin is only about 20% of that found with injectable gold compounds. Studies in animals suggest that auranofin binds to tissues to a lesser extent than does gold sodium thiomalate. After cessation of

treatment, the half-life of gold in the body is about 80 days (*see* Chaffman *et al.*, 1984). Auranofin is predominantly excreted in the feces.

Preparations, Routes of Administration, and Dosage. *Aurothioglucose* (SOLGANAL) contains approximately 50% gold. Although it is water soluble, it is employed as a sterile suspension in a suitable fixed oil. The commercial preparation contains 50 mg/ml. *Gold sodium thiomalate* (MYOCHRYSINE) also contains approximately 50% gold and is very soluble in water. It is available as a sterile aqueous solution for injection. Both compounds should be administered intramuscularly.

The optimal intramuscular dosage schedule for the treatment of rheumatoid arthritis is still debated. Moreover, some rheumatologists use the same dosage regimen for either compound while others do not. The usual dose is 10 mg of either gold compound in the first week as a test dose, followed by 25 mg in the second and third weeks. Thereafter, either 25 to 50 mg (gold sodium thiomalate) or 50 mg (aurothioglucose) is administered at weekly intervals until the cumulative dose reaches 1 g. A favorable response may not be evident for a few months. If a remission occurs, treatment is continued but the dose is reduced or the dosage interval is increased. For example, 25 to 50 mg may be administered every 2 weeks for up to 20 weeks, followed by a dose every 3 weeks for an additional 18 weeks; thereafter a monthly-interval schedule may be followed for an indefinite period. If neither significant toxicity nor clinical response is apparent after the administration of 1 g of gold sodium thiomalate, a gradual increase in dosage may be considered; the weekly dose of this compound should not exceed 100 mg.

Auranofin (RIDAURA) contains about 29% gold and is available in 3-mg capsules for oral administration. For active rheumatoid arthritis, the daily dosage is 6 mg, which is given in one or two portions; some patients may require 9 mg daily in three divided doses. This higher dosage should not be instituted until the lower dosage has been given for 6 months, and therapy should be discontinued after 3 additional months if the response is still inadequate. Although patients have been maintained successfully on auranofin for several years, the optimal duration of therapy has not been determined.

Toxic Effects. The most common toxic effects that are associated with the therapeutic use of gold are those that involve the skin and the mucous membranes, usually of the mouth. These occur in about 15% of all patients. While clearly dose related, these effects do not correlate well with the concentration of gold in plasma (*see* Rothermich, in Symposium, 1983a). Cutaneous reactions may vary in severity from simple erythema to severe exfoliative dermatitis. Lesions of the mucous membranes include stomatitis, pharyngitis, tracheitis, gastritis, colitis, and vaginitis; glossitis is fairly common. As with silver, a gray-to-blue pigmentation (chrysiasis) may occur in the skin and mucous membranes, especially in areas exposed to light.

The kidneys may be affected to some degree in 5 to 8% of patients receiving gold, and transient and mild proteinuria occurs in more than 50% of patients during therapy. Heavy albuminuria and microscopic hematuria occur in 1 to 3% of cases. The site of damage is usually the proximal tubules. In addition, a gold-induced nephrosis can occur; the predominant lesion is membranous glomerulonephritis that is usually reversible.

Severe blood dyscrasias may also occur. Thrombocytopenia is observed in about 1% of patients. Most often this appears to be an immunological disturbance that results in an accelerated degradation of platelets. Occasionally the thrombocytopenia is a consequence of effects upon the bone marrow. In either case, withdrawal of the drug usually leads to recovery, but fatalities have occurred. Leukopenia, agranulocytosis, and aplastic anemia may also occur; aplastic anemia is rare but often fatal. When panmyelopathy results from aurotherapy, the concentrations of coproporphyrin and δ-aminolevulinic acid (δ-ALA) in urine may increase, as in lead poisoning. Eosinophilia is common, and many rheumatologists temporarily discontinue gold therapy when it occurs.

Gold may cause a variety of other severe toxic reactions, including encephalitis, peripheral neuritis, hepatitis, pulmonary infiltrates, and nitritoid (vasomotor) crisis. Fortunately, the incidence of serious reactions is low, and they generally are the result of failure to discontinue therapy when earlier, less serious symptoms occur.

Auranofin appears to be better tolerated than are the injectable gold compounds, and the incidence and severity of mucocutaneous and hematological side effects are less. However, auranofin produces a high incidence of gastrointestinal disturbances, which are sometimes troublesome and lead to discontinuation of therapy by about 5% of patients receiving the drug. About half of patients have a change in bowel habits

(more frequent or loose stools often associated with abdominal cramping). Proteinuria is much less common with auranofin than with parenteral preparations, and the incidence of nephrotoxicity may also be less.

Avoidance and Treatment. Regular examination of the skin, buccal mucosa, urine, and blood, including cell and platelet counts, should be made. It is the practice in many arthritis clinics to initiate therapy with small doses of gold and to increase the dose gradually. Although untoward effects are not eliminated by this procedure, the severity of the reactions that occur early is somewhat reduced. If an untoward response occurs, therapy should be withheld until it subsides completely. If the reaction is a rash or stomatitis, antihistamines and glucocorticoids may be administered, the latter systemically and/or topically. Glucocorticoids are also indicated in gold-induced nephrosis.

If the reaction to gold therapy is not serious, injections of parenteral gold preparations may be cautiously resumed 2 or 3 weeks after the toxic reaction has subsided. Maintenance dosage should be two thirds to three fourths that previously planned. However, many experts decline to use the drug again, once toxicity has occurred. For auranofin, a decrease in dosage can also be attempted, but therapeutic responses may not be obtained.

If a severe reaction to gold occurs or if the above-mentioned steps fail to control the toxic effects, treatment with dimercaprol or penicillamine should be instituted. The administration of dimercaprol may shorten a therapeutic remission induced by gold.

Therapeutic Uses. Gold compounds find their chief therapeutic application in rheumatoid arthritis. Although these compounds can cause serious toxicity, they are among the most effective agents available for the treatment of rapidly progressive forms of the disease. Since other effective drugs (*e.g.*, penicillamine, methotrexate) can produce significantly more toxicity during long-term therapy, gold compounds are usually chosen to initiate therapy of rheumatoid arthritis when the goal is to attempt to halt its progression (*see* Rothermich, in Symposium, 1983a; Symposium, 1986c; Tsokos, 1987).

At present, gold is used in early, active arthritis that progresses despite an adequate regimen of aspirin-like drugs, rest, and physical therapy. Both subjective and objective manifestations of rheumatoid arthritis are improved. Gold compounds often arrest the progression of the disease in involved joints, at least temporarily; prevent involvement of unaffected joints; improve grip strength and morning stiffness; and decrease the erythrocyte sedimentation rate and abnormal plasma glycoprotein and fibrinogen levels. Gold should not be used if the disease is mild and is usually of little benefit when the disease is advanced. It has been estimated that chrysotherapy will induce a protracted remission in about 15% of patients, improve symptoms in 60 to 70% of patients, and must be discontinued in 15 to 20% of patients because of toxicity; about 10 to 15% of patients do not respond. The duration of the remission after discontinuation of treatment with gold is extremely variable (from 1 to 18 months). Although the recurrence is usually not as severe as the original disease and the majority of patients respond favorably to a second course of gold therapy, many rheumatologists prefer to continue treatment indefinitely without waiting for a relapse to occur. After 3 to 6 years of either continuous or discontinuous therapy, more than 50% of patients who had responded initially have terminated their treatment because of relapse or delayed toxicity (*see* Pinals, in Symposium, 1983d).

Therapy with gold is sometimes beneficial in juvenile rheumatoid arthritis, palindromic rheumatism, psoriatic arthritis, Sjögren's syndrome, nondisseminated lupus erythematosus, and pemphigus. Except for injectable preparations in the treatment of juvenile forms of arthritis, the use of gold in these conditions has not been approved in the United States.

Contraindications. Gold therapy is contraindicated in patients with renal disease, hepatic dysfunction or a history of infectious hepatitis, or hematological disorders. Gold should not be readministered to patients who have developed severe hematological or renal toxicity during a course of chrysotherapy; auranofin should not be administered after the occurrence of several additional gold-induced disorders, including pulmonary fibrosis, necrotizing enterocolitis, and exfoliative dermatitis. Gold is contraindicated during pregnancy or breast feeding. Patients who have recently had radiation should not receive gold because of its depressant action on hematopoietic tissue. Concomitant use of antimalarials, immunosuppressants, phenylbutazone, or oxyphenbutazone is contraindicated because of the potential of these drugs to cause blood dyscrasias. Urticaria, eczema, and colitis are also considered to be contraindications to the use of the metal. Finally, gold is poorly tolerated by elderly individuals.

OTHER DRUGS FOR RHEUMATOID ARTHRITIS

In addition to nonsteroidal antiinflammatory agents and gold, other drugs are also used for the treatment of rheumatoid arthritis. These include immunosuppressive agents, glucocorticoids, penicillamine, and hydroxychloroquine. With the exception of glucocorticoids, these drugs resemble gold salts in that they do not possess antiinflammatory or analgesic properties and their therapeutic effects become evident only after several weeks or months of treatment. They are generally reserved for patients who are refractory to therapeutic regimens that include rest, physiotherapy, and aspirin-like drugs, and in many instances, for those who do not tolerate or respond to treatment with gold. Although they are often grouped with gold as so-

called disease-modifying antiarthritic drugs, these compounds are unlikely to induce remissions and are less apt to retard synovial erosion than is gold in patients with severe active rheumatoid arthritis (*see* Ward, 1988).

Although glucocorticoids can often produce dramatic symptomatic improvement, they do not arrest the progress of rheumatoid arthritis and are used only as adjuvants to other treatment because of their long-term toxicity (*see* Chapter 60). Immunosuppressants sometimes relieve joint inflammation when chrysotherapy has failed, but each of these drugs has its unique and significant toxicities (*see* Chapter 53). Of the cytotoxic immunosuppressants, only azathioprine and low oral doses of methotrexate have been approved for the treatment of rheumatoid arthritis; the use of cyclosporine, a novel immunosuppressant, is under investigation.

Even though their mechanisms of action are not understood, hydroxychloroquine and penicillamine are useful, orally effective alternatives to gold in the treatment of patients with early, mild, and nonerosive disease (*see* Ward, 1988). The latter drug is more apt to produce serious toxicity, including various cutaneous lesions, blood dyscrasias, and a number of autoimmune syndromes (*see* Chapter 66). Therapy with penicillamine is initiated with single daily doses of 125 to 250 mg; the dosage is gradually increased at 1- to 3-month intervals to a maximum of 1 to 1.5 g per day. Many patients will respond to less than 500 to 750 mg per day.

Hydroxychloroquine shares the toxicity of other 4-aminoquinoline antimalarials (*see* Chapter 41). Of greatest concern during the long-term treatment of rheumatoid arthritis is the danger of producing irreversible retinal damage. The risk of corneal deposits and ocular toxicity appears to be less for hydroxychloroquine than for chloroquine at the usual antirheumatic doses (*see* Easterbrook, 1988; Rynes, 1988). Therapy is initiated with 400 to 600 mg of hydroxychloroquine sulfate per day, taken with food or milk. After a satisfactory response is obtained (usually within 1 to 3 months), the daily dose is reduced to 200 to 400 mg. Ophthalmological examinations should be performed before treatment is begun and every 3 months thereafter.

DRUGS EMPLOYED IN THE TREATMENT OF GOUT

An acute attack of gout occurs as a result of an inflammatory reaction to crystals of sodium urate (the end product of purine metabolism in man) that are deposited in the joint tissue. The inflammatory response involves local infiltration of granulocytes, which phagocytize the urate crystals. Lactate production is high in synovial tissues and in the leukocytes associated with the inflammatory process, and this favors a local decrease in pH that fosters further deposition of uric acid.

Several therapeutic strategies can be used to counter attacks of gout. Uricosuric drugs increase the excretion of uric acid, thus reducing concentrations in plasma. Colchicine is specifically efficacious in gout, probably secondary to an effect on the mobility of granulocytes. Allopurinol is a selective inhibitor of the terminal steps of the biosynthesis of uric acid. Although prostaglandins may be implicated in the pain and inflammation, there is no evidence that they contribute to the pathogenesis of gout; nevertheless, aspirin-like drugs usually afford symptomatic relief, and some of them are uricosuric as well (*see* Gibson, in Lewis and Furst, 1987).

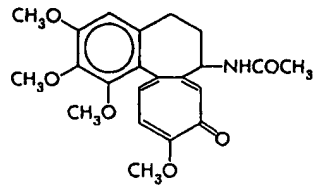
The pharmacology of aspirin-like drugs is described in the previous section. Discussion in this section is limited to colchicine, allopurinol, and the clinical use of the uricosuric agents. The basic pharmacology of uricosuric drugs is presented in Chapter 30. A useful volume on uric acid that contains major sections on the pathogenesis and therapy of gout is that edited by Kelley and Weiner (1978).

COLCHICINE

Colchicine is a unique antiinflammatory agent in that it is largely effective only against gouty arthritis. It provides dramatic relief of acute attacks of gout and is an effective prophylactic agent against such attacks.

History. Colchicine is an alkaloid of *Colchicum autumnale* (autumn crocus, meadow saffron). Although the poisonous action of colchicum was known to Dioscorides, preparations of the plant were not recommended for pain of articular origin until the sixth century A.D. Colchicum was introduced for the therapy of acute gout by von Störck in 1763, and its specificity for this syndrome soon resulted in its incorporation in a number of "gout mixtures" popularized by charlatans. Benjamin Franklin, himself a sufferer from gout, is reputed to have introduced colchicum therapy in the United States. The alkaloid colchicine was isolated from colchicum in 1820 by Pelletier and Caventou.

Chemistry. The structural formula of colchicine is as follows:



Colchicine

The structure–activity relationship of colchicine and related agents has been discussed by Wallace (1961).

Pharmacological Properties. The antiinflammatory effect of colchicine in acute gouty arthritis is relatively selective for this disorder. Colchicine is only occasionally effective in other types of arthritis; it is not an analgesic and does not provide relief of other types of pain.

Colchicine is an antimitotic agent and is widely employed as an experimental tool in the study of cell division and function.

Effect in Gout. Colchicine does not influence the renal excretion of uric acid or its concentration in blood. By virtue of its ability to bind to microtubular protein (tubulin), colchicine interferes with the function of the mitotic spindles and causes depolymerization and disappearance of the fibrillar microtubules in granulocytes and other motile cells. This action is apparently the basis for the beneficial effect of colchicine, namely, the inhibition of the migration of granulocytes into the inflamed area. This reduces the release of lactic acid and proinflammatory enzymes that occurs during phagocytosis and breaks the cycle that leads to the inflammatory response. However, there are a number of apparently contradictory observations that cannot be accommodated by this simple hypothesis (*see* Wallace and Ertel, 1978).

Neutrophils exposed to urate crystals ingest them and produce a glycoprotein, which may be the causative agent of acute gouty arthritis. Injected into joints, this substance produces a profound arthritis that is histologically indistinguishable from that caused by direct injection of urate crystals. Although it does not prevent phagocytosis of urate crystals, colchicine appears to prevent the elaboration by leukocytes of the glycoprotein that causes the joint pain and inflammation.

Effect on Cell Division. Colchicine can arrest plant and animal cell division *in vitro* and *in vivo*. Mitosis is arrested in metaphase, due to failure of spindle formation. Cells with the highest rates of division are affected earliest. High concentrations may completely prevent cells from entering mitosis, and they often die. The action is also characteristic of the vinca alkaloids (vincristine and vinblastine), podophyllotoxin, and griseofulvin.

Other Effects. Colchicine inhibits the release of histamine-containing granules from mast cells, the secretion of insulin from beta cells of pancreatic islets, and the movement of melanin granules in melanophores; all of these processes may involve the translocation of granules by the microtubular system.

Colchicine also exhibits a variety of other pharmacological effects. It lowers body temperature, increases the sensitivity to central depressants, depresses the respiratory center, enhances the response to sympathomimetic agents, constricts blood vessels, and induces hypertension by central vasomotor stimulation. It enhances gastrointestinal activity by neurogenic stimulation but depresses it by a direct effect, and alters neuromuscular function.

Pharmacokinetics and Metabolism. Colchicine is rapidly absorbed after oral administration, and peak concentrations occur in plasma by 0.5 to 2 hours. Large amounts of the drug and metabolites enter the intestinal tract in the bile and intestinal secretions, and this fact, plus the rapid turnover of intestinal epithelium, probably explains the prominence of intestinal manifestations in colchicine poisoning. The kidney, liver, and spleen also contain high concentrations of colchicine, but it is apparently largely excluded from heart, skeletal muscle, and brain. The drug can be detected in leukocytes and in the urine for at least 9 days after a single intravenous dose.

Colchicine is metabolized to a mixture of compounds *in vitro*. Most of the drug is excreted in the feces; however, in normal individuals, 10 to 20% of the drug is excreted in the urine. In patients with liver disease, hepatic uptake and elimination are reduced and a greater fraction of the drug is excreted in the urine.

Toxic Effects. Colchicine is well tolerated in moderate dosage. The most common side effects reflect the action of the drug on the rapidly proliferating epithelial cells in the gastrointestinal tract, especially in the jejunum. Nausea, vomiting, diarrhea, and abdominal pain are the most common and earliest untoward effects of colchicine overdosage. To avoid more serious toxicity, administration of the drug is discontinued as soon as these symptoms occur. There is a latent period of several hours or more between the administration of the drug and the onset of symptoms. This interval is not altered by dosage or route of administration. For this reason, and because of individual variation, adverse effects may be unavoidable during an initial course of medication with colchicine. However, the patient often remains relatively consistent in his response to the drug, and therefore toxicity can be minimized or avoided during subsequent courses of therapy. The drug is equally effective when given intravenously; the onset of the therapeutic effect may be faster, and the gastrointestinal side effects may be almost completely avoided.

In acute poisoning with colchicine, there is hemorrhagic gastroenteritis, extensive vascular damage, nephrotoxicity, muscular depression, and an ascending paralysis of the CNS.

Colchicine produces a temporary leukopenia that is soon replaced by a leukocytosis, sometimes due to a striking increase in the number of basophilic granulocytes. The site of action is apparently directly on the bone marrow. Myopathy and neuropathy have also been noted with colchicine treat-

ment, especially in patients with decreased renal function (Kuncl *et al.*, 1987). Long-term administration of colchicine entails some risk of agranulocytosis, aplastic anemia, myopathy, and alopecia; azoospermia has also been described.

Preparations. *Colchicine* is available as 0.5- and 0.6-mg tablets; they should be stored in tight, light-resistant containers. A sterile solution (0.5 mg/ml) is also available for injection.

Therapeutic Uses. Colchicine provides dramatic relief from acute attacks of gout. The effect is sufficiently selective that the drug has been used for diagnostic purposes, but the test is not infallible. Colchicine also has an established role to prevent and to abort acute attacks of gout (*see* Rodnan, 1982; Talbott, in Symposium, 1983a). However, its toxicity and the availability of alternative agents that may be less toxic have lessened its usefulness (*see* Roberts *et al.*, 1987).

Acute Attacks. When colchicine is given promptly within the first few hours of an attack, less than 5% of patients fail to obtain relief. Pain, swelling, and redness abate within 12 hours and are completely gone in 48 to 72 hours. The usual doses are 0.5 to 1.2 mg, taken at intervals of 1 to 2 hours until either the pain disappears or gastrointestinal symptoms develop. The total dose usually required to alleviate an attack is 4 to 10 mg, and the latter amount should not be exceeded. Opioids or other drugs may be required for the diarrhea. In subsequent attacks, the patient may be able to stop medication short of the amount that causes toxic reactions. Colchicine can be administered intravenously, and there may be distinct advantages to this route for some patients (*see* Roberts *et al.*, 1987; Wallace and Singer, 1988). Although a number of regimens have been used, a single dose of 2 mg, diluted in 10 to 20 ml of 0.9% sodium chloride solution, is usually adequate; a total dose of 4 mg should not be exceeded. To avoid cumulative toxicity, treatment with colchicine should not be repeated within 3 (oral) or 7 (intravenous) days.

Great care should be exercised in prescribing colchicine for elderly patients, and for those with cardiac, renal, hepatic, or gastrointestinal disease. In these patients and in those who do not tolerate or respond to colchicine, indomethacin or another aspirin-like drug is preferred.

Prophylactic Uses. For patients with chronic gout, colchicine has established value as a prophylactic agent, especially when there is frequent recurrence of attacks. Prophylactic medication is also indicated upon initiation of long-term medication with allopurinol or the uricosuric agents, since acute attacks often increase in frequency during the early months of such therapy.

The prophylactic dose of colchicine depends upon the frequency and severity of prior attacks. As little as 0.5 mg two to four times a week may suffice; as much as 1.8 mg per day may be required by some patients. Colchicine should be taken in larger abortive doses immediately upon the first twinge of articular pain or the appearance of any prodrome of an acute attack. Before and after surgery in patients with gout, colchicine should be given for 3 days (0.5 or 0.6 mg, three times a day); this greatly reduces the very high incidence of acute attacks of gouty arthritis precipitated by operative procedures.

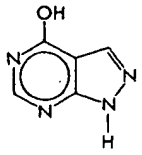
Daily administration of colchicine is useful for the prevention of attacks of familial Mediterranean fever (familial paroxysmal polyserositis) and for prevention and treatment of amyloidosis in such patients (Zemer *et al.*, 1986). Colchicine appears to benefit patients with primary biliary cirrhosis, although the underlying disease may not be altered (Bodenheimer *et al.*, 1988). Colchicine has been approved as an orphan drug to arrest the progression of neurological disability caused by multiple sclerosis. It has also been employed to treat a variety of skin disorders, including psoriasis and Behçet's syndrome (*see* Aram, 1983).

ALLOPURINOL

Allopurinol is effective for the treatment of both the primary hyperuricemia of gout and that secondary to hematological disorders or antineoplastic therapy. In contrast to the uricosuric agents that increase the renal excretion of urate, allopurinol inhibits the terminal steps in uric acid biosynthesis. Since overproduction of uric acid is a contributing factor in most patients with gout and a characteristic of most types of secondary hyperuricemia, allopurinol represents a rational approach to therapy.

History. The introduction of allopurinol by Hitchings, Elion, and associates provides an elegant example of the development of a drug on a rational biochemical basis. Originally synthesized as a candidate for an antineoplastic agent, allopurinol was found to lack antimetabolite activity but it proved to be a substrate for and an inhibitor of xanthine oxidase. Allopurinol delays inactivation of mercaptopurine by xanthine oxidase and reduces the plasma concentration and renal excretion of uric acid. Subsequent clinical study for treatment of gout by Rundles and coworkers was successful and quickly confirmed (*see* Elion, 1978).

Chemistry and Pharmacological Properties. Allopurinol, an analog of hypoxanthine, has the following structural formula:



Allopurinol

Both allopurinol and its primary metabolite, alloxanthine (oxypurinol), are inhibi-

tors of xanthine oxidase. Inhibition of this enzyme accounts for the major pharmacological effects of allopurinol (*see* Elion, 1978).

In man, uric acid is formed primarily by the xanthine oxidase–catalyzed oxidation of hypoxanthine and xanthine. At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme; at high concentrations, it is a noncompetitive inhibitor. Alloxanthine, the metabolite of allopurinol formed by the action of xanthine oxidase, is a noncompetitive inhibitor of the enzyme; the formation of this compound, together with its long persistence in tissues, is undoubtedly responsible for much of the pharmacological activity of allopurinol. Inhibition of uric acid biosynthesis reduces its plasma concentration and urinary excretion and increases the plasma concentrations and renal excretion of the more soluble oxypurine precursors.

In the absence of allopurinol, the urinary content of purines is almost solely uric acid. During treatment with allopurinol, the urinary purines are divided among hypoxanthine, xanthine, and uric acid. Since each has its independent solubility, the concentration of uric acid in plasma is reduced without exposing the urinary tract to an excessive load of uric acid and the likelihood of calculus formation. By lowering the uric acid concentration in plasma below its limit of solubility, allopurinol facilitates the dissolution of tophi and prevents the development or progression of chronic gouty arthritis. The formation of uric acid stones virtually disappears with therapy, and this prevents the development of nephropathy. The incidence of acute attacks of arthritis may increase during the early months of therapy but is subsequently reduced.

Tissue deposition of xanthine and hypoxanthine usually does not occur during allopurinol therapy because the renal clearance of the oxypurines is rapid; their plasma concentrations are only slightly increased and do not exceed their solubility. Although xanthine constitutes about 50% of total oxypurine excreted in the urine and is relatively insoluble, xanthine stone formation during allopurinol therapy has occurred only occasionally in patients with very high uric acid production prior to treatment. The risk can be minimized by alkalinization of the urine and by increasing the daily fluid intake during the administration of allopurinol. In some patients, the allopurinol-induced increase in excretion of oxypurines is less than the reduction in uric acid excretion; this disparity is primarily a result of reutilization of oxypurines and feedback inhibition of *de-novo* purine biosynthesis.

Pharmacokinetics and Metabolism. Allopurinol is absorbed relatively rapidly after oral ingestion, and peak plasma concentration is reached within 30 to 60 minutes. About 20% is excreted in the feces in 48 to 72 hours, presumably as unabsorbed drug. Allopurinol is rapidly cleared from plasma with a half-time of 2 to 3 hours, primarily by conversion to alloxanthine. Less than 10% of a single dose or about 30% of the drug ingested during long-term medication is excreted unchanged in the urine. Self-inhibition of the metabolism of allopurinol to alloxanthine explains this dose-dependent elimination. Alloxanthine is slowly excreted in the urine by the net balance of glomerular filtration and probenecid-sensitive tubular reabsorption. The plasma half-life of alloxanthine is 18 to 30 hours in patients with normal renal function and increases in proportion to the reduction of glomerular filtration in patients with renal impairment.

Allopurinol and its metabolite alloxanthine are distributed in total tissue water, with the exception of brain, in which their concentration is about one third that in other tissues. Neither compound is bound to plasma proteins. The plasma concentrations of the two compounds do not correlate well with therapeutic or toxic effects.

Drug Interactions. Interactions between allopurinol and probenecid and other uricosuric agents and those between allopurinol and mercaptopurine (and its derivative azathioprine) have been alluded to above. Allopurinol may also interfere with the hepatic inactivation of other drugs, including the oral anticoagulant agents. Although the effect is variable and of clinical significance only in some patients, increased monitoring of prothrombin activity is recommended in patients receiving both medications.

Whether the increased incidence of skin rash in patients receiving concurrent allopurinol–ampicillin medication, compared with that observed when these agents are administered individually, should be ascribed to allopurinol or to hyperuricemia remains to be established. Hypersensitivity reactions have been reported in patients with compromised renal function who are receiving a combination of allopurinol and a thiazide diuretic. The concomitant administration of allopurinol and theophylline leads to increased accumulation of an active metabolite of theophylline, 1-methylxanthine; the concentration of theophylline in plasma may also be increased.

Toxic Effects. Allopurinol is well tolerated by most patients. The most common adverse effects are hypersensitivity reactions. They may occur even after months or years of medication. The effects usually subside within a few days after medication is discontinued. Serious reactions preclude further use of the drug.

Attacks of acute gout may occur more frequently during the initial months of allopurinol medication and may require con-

current prophylactic therapy with colchicine (*see* above).

The cutaneous reaction caused by allopurinol is predominantly a pruritic, erythematous, or maculopapular eruption, but occasionally the lesion is exfoliative, urticarial, or purpuric. Fever, malaise, and muscle aching may also occur. Such effects are noted in about 3% of patients with normal renal function but more frequently in those with renal impairment.

Transient leukopenia or leukocytosis and eosinophilia are rare reactions but may require cessation of therapy. Hepatomegaly and elevated levels of transaminase activities in plasma may also occur. There have been isolated reports of peripheral neuritis, bone-marrow depression, and cataracts. Eosinophilia with epidermal necrolysis has resulted in renal failure.

Undesirable side effects such as headache, drowsiness, nausea, vomiting, vertigo, diarrhea, and gastric irritation occur occasionally but usually do not require that therapy be stopped.

Preparations, Route of Administration, and Dosage. *Allopurinol* (ZYLOPRIM, others) is available as 100- and 300-mg tablets for oral use.

For control of hyperuricemia in gout, the aim of therapy is to reduce the plasma uric acid concentration below 6 mg/dl (360 μM). Medication must not be initiated during an acute attack of gouty arthritis, and it is started at low doses to minimize the risk of precipitating such attacks. Concurrent prophylactic administration of colchicine is also recommended during and sometimes beyond the initial months of therapy. Fluid intake should be sufficient to maintain daily urinary volume above 2 liters; slightly alkaline urine is preferred. An initial daily dose of 100 mg is increased by 100-mg increments at weekly intervals to a maximum of 800 mg per day. The usual daily maintenance dose for adults is 200 to 300 mg for those with mild gout and 400 to 600 mg for patients with moderately severe tophaceous gout. Daily doses in excess of 300 mg should be given in divided portions. Dosage must be reduced in patients with renal impairment in proportion to the reduction in glomerular filtration (Hande *et al.*, 1984); for example, no more than 200 mg per day should be used in patients whose creatinine clearance is 10 to 20 ml/min.

In the treatment of secondary hyperuricemias, as for the prevention of uric acid nephropathy during vigorous treatment of certain neoplastic diseases, a dose of 600 to 800 mg daily for 2 to 3 days is advisable, together with a high fluid intake. In children with secondary hyperuricemias associated with malignancies, the usual daily dose is 150 to 300 mg, depending upon age.

Therapeutic Uses. Allopurinol provides effective therapy for both the primary hyperuricemia of gout and that secondary to polycythemia vera, myeloid metaplasia, or other blood dyscrasias.

Allopurinol is contraindicated in patients who have exhibited serious adverse effects from the medication, nursing mothers, and children, except those with malignancy or certain inborn errors of purine metabolism.

In gout, allopurinol is generally used in the severe chronic forms characterized by one or more of the following conditions: gouty nephropathy, tophaceous deposits, renal urate stones, impaired renal function, or hyperuricemia not readily controlled by the uricosuric drugs.

When given in effective doses and over prolonged periods, allopurinol fosters resorption of tophi and improvement of joint function in patients with tophaceous gout. By decreasing the amount of uric acid excreted and thereby preventing the development of nephrolithiasis, allopurinol eliminates the major cause of renal injury in patients with gout. It also appears likely that gouty nephropathy can be reversed by the drug if therapy is begun at a reasonably early stage, before renal function is severely compromised; however, there is little evidence of improvement in advanced renal disease.

Since attacks of acute gout occur in patients taking allopurinol, particularly during the initial stage of treatment, colchicine is used prophylactically when therapy is begun and continued if necessary to prevent such attacks. Concurrent allopurinol and uricosuric therapy is also employed occasionally, especially in patients with large tophaceous deposits in whom it is desirable both to reduce production and to increase elimination of uric acid. Such combined medication is valid, but interaction between these drugs is sometimes complex. The uricosuric agents increase the renal excretion of alloxanthine and thus cause a reduction in allopurinol effect. Conversely, allopurinol may delay elimination of probenecid and increase its concentration in plasma.

Allopurinol is also administered prophylactically to reduce the hyperuricemia and to prevent urate deposition or renal calculi in patients with leukemias, lymphomas, or other malignancies, particularly when antineoplastic or radiation therapy is initiated. Allopurinol inhibits the enzymatic inactivation of mercaptopurine by xanthine oxidase. Thus, when allopurinol is used concomitantly with oral mercaptopurine or azathioprine, dosage of the antineoplastic agent must be reduced to one fourth to one third of the usual dose. The risk of bone-marrow suppression is also increased when allopurinol is administered with cytotoxic agents that are not metabolized by xanthine oxidase, particularly cyclophosphamide.

The iatrogenic hyperuricemia sometimes induced by the thiazides and other drugs can be prevented or reversed by concurrent allopurinol medication, although this is rarely necessary. Allopurinol is also useful in lowering the high plasma concentrations of uric acid in patients with Lesch–Nyhan syndrome and thereby prevents the complications resulting from hyperuricemia; there is no evidence that it alters the progressive neuro-

logical and behavioral abnormalities characteristic of the disease.

CLINICAL USE OF URICOSURIC AGENTS

As described in Chapter 30, the uricosuric agents act directly on the renal tubule to increase the rate of excretion of uric acid. Although many agents share this property, only a few, primarily probenecid and sulfinpyrazone, are used clinically as uricosuric agents. Benzbromarone is not available for general use in the United States but is used elsewhere, especially in patients with renal insufficiency. In the clinical use of uricosuric drugs, it must be kept in mind that they can alter the plasma binding, distribution, and renal excretion of other organic acids, whether these are naturally occurring substances or drugs and drug metabolites.

Gout. The use of probenecid and sulfinpyrazone for the mobilization of uric acid in chronic gout is well established. In about two thirds of patients, these agents cause uric acid to be excreted at a rate sufficient to exceed that of formation and thereby promptly lower the plasma uric acid concentration. Although the intravenous administration of large doses of these drugs can cause a fivefold to sevenfold increase in the renal clearance of urate, continuous oral administration to patients with tophaceous gout approximately doubles the daily excretion of urates. In such patients, continued administration prevents the formation of new tophi and causes gradual shrinkage, or even disappearance, of old tophi. In gouty arthritis, there is a reduction in the swelling of chronically enlarged joints and a dramatic degree of rehabilitation may be achieved in patients who suffer severe pain and limitation of joint movement. In patients who do not respond well to uricosuric agents because of impaired renal function, allopurinol is especially useful, as described above. In patients with gouty nephropathy, allopurinol offers additional advantage over the uricosuric agents in that the daily excretion of uric acid is reduced rather than increased. Its administration is compatible with the simultaneous use of the uricosuric agents if necessary.

Neither the uricosuric agents nor allopurinol alters the course of acute attacks of gout or supplants the use of colchicine and antiinflammatory agents in their management. Indeed, the acute attacks may increase in frequency or severity during the early months of therapy when urate is being mobilized from affected joints. Therefore, therapy with uricosuric agents should not be initiated during an acute attack but may be continued if already begun. Colchicine in small doses (0.5 to 1.8 mg per day) may be administered at this period (or at any time) to reduce the frequency of attacks. When an acute attack occurs, it is treated with full doses of colchicine or an antiinflammatory drug such as indomethacin or naproxen. The use of salicylates is contraindicated because they antagonize the action of probenecid and sulfinpyrazone.

In the treatment of gout, the uricosuric drugs are given continually in the lowest dose that will maintain satisfactory plasma uric acid concentrations. Since the pK_a of uric acid is 5.6 and the solubility of the undissociated form is very low, maintaining the output of a large volume of alkaline urine minimizes its intrarenal deposition. This precaution is essential during the early weeks of therapy when uric acid excretion is large, especially in patients with a history of renal disease associated with the passage of urate stones or gravel. Eventual improvement in renal function in patients with gouty nephropathy has been reported, but it is uncommon. The use of allopurinol permits a more favorable prognosis in such patients. (For detailed evaluations of uricosuric agents, *see* Boss and Seegmiller, 1979; Rodnan, 1982.)

Other Hyperuricemic States. Uricosuric agents are useful for the control of the hyperuricemia resulting from the use of the cytotoxic antineoplastic agents or from diseases that involve accelerated formation and destruction of blood cells. Uricosuric agents are also rarely required to manage hyperuricemia in other settings, such as therapy with diuretics, levodopa, and ethambutol, and in certain disease states, including toxemia of pregnancy, diabetic ketosis, and uremia. The hyperuricemia usually remains asymptomatic, but attacks of gout or renal precipitation of urate may occur.

Selection of Agents for the Treatment of Gout and Hyperuricemia. Acute attacks of gout are effectively treated with colchicine or an aspirin-like drug, as discussed above. After the acute arthritis has responded to therapy, the patient should be evaluated in order to select a rational regimen for long-term management. Elevated concentrations of uric acid in plasma and the observation of crystals of urate in the aspirated fluid from an affected joint establish the diagnosis of hyperuricemia and symptomatic gout. When evaluated on a diet that is low in purines, patients with hyperuricemia can be categorized with regard to quantities of uric acid excreted in the urine. About 80 to 90% of such individuals excrete less than 600 mg of uric acid daily; the remainder excrete more than this amount due to excessive synthesis of urate. The former group can be managed effectively with uricosuric agents; the latter, however, is logically treated with allopurinol. If deposits of urate are evident as tophi, renal stones, or renal insufficiency, allopurinol is generally the preferred drug. During the first several months of treatment with allopurinol, colchicine may be given simultaneously to prevent acute attacks of gout. Patients with mild-to-moderate hyperuricemia (7 to 9 mg/dl) (420 to 530 μM) who do not have arthritis should be advised to drink large amounts of fluids and follow a diet low in purines. Drug-induced hyperuricemia is most commonly caused by diuretics (*see* Chapter 28); acute attacks of gout are only rarely caused by such agents. However, hyperuricemia that accompanies chemotherapy or radiotherapy for various neoplasms may be considerably more severe and is usually treated prophylactically with allopurinol and hydration.

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